21038

NATIONAL LIBRARY
OTTAWA

CANADA

BIBLIOTHÈQUE NATIONALE
OTTAWA

NAME OF AUTHOR Roger A. Jones

TITLE OF THESIS Synthesis of Deoxy and
Unsaturated Nucleosides from
Ribonucleoside 2', 3'-O-orthoesters

UNIVERSITY U. of Alberta

DEGREE FOR WHICH THESIS WAS PRESENTED PhD

YEAR THIS DEGREE GRANTED 1974

Permission is hereby granted to THE NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

(Signed) Roger A. Jones

PERMANENT ADDRESS:

448 Atlantic Ave
York, Pennsylvania
U.S.A. 17404

DATED May 1 1974

NL-91 (10-68)

THE UNIVERSITY OF ALBERTA

SYNTHESIS OF DEOXY AND UNSATURATED NUCLEOSIDES FROM RIBONUCLEOSIDE 2',3'-O-ORTHOESTERS

BY

© ROGER A. JONES

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
SPRING, 1974

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled [illegible] and Unsaturated Nucleosides from [illegible] 2',3'-O-Orthoesters

submitted by Roger A. Jones

in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Supervisor

External Examiner

Date May 10, 1974

ABSTRACT

Treatment of 2',3'-*O*-methoxyethylideneadenosine with pivalyl chloride and sodium iodide in pyridine solution was found to give good yields of 2'- or 3'-iodo-2'- or 3'-deoxy nucleosides. The products were found to bear a complex 3'- or 2'-*O*-"enolester" function (4,4-dimethyl-3-pivaloxypent-2-enoate) in addition to the expected 6-*N*- and 5'-*O*-pivalyl groups. The novel formation of this function from an orthoester was studied and a rationalization suggested. In this regard an interesting adenosine 2',3'-*O*-pivalylketene acetal was isolated and shown to function as an intermediate. Treatment of triethyl orthoacetate with pivalyl chloride-sodium iodide-pyridine gave ethyl 4,4-dimethyl-3-pivaloxypent-2-enoate. This compound was also obtained from sodium ethoxide treatment of one of the nucleoside enolester derivatives. Some aspects of the mass spectral fragmentation of these enolester derivatives are discussed.

Chromatography on carbon has been utilized to develop a facile separation of 6-*N*-pivalamido-9-(3-iodo-3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)purine and the corresponding 2'-iodo-2'-deoxyarabinofuranosyl isomer. Small amounts of 6-*N*-pivalamido-9-(3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-

dimethyl-3-pivaloxypent-2-enoyl]-β-D-*glycero*-pent-3-enofuranosyl)purine and 6-N-pivalamido-9-(5-pivaloxymethyl-2-furanyl)purine were also isolated. Crystallization using a diffusion method was used in many cases and was found to be of exceptional value with these compounds. This technique involves allowing a volatile solvent (in which the compound is insoluble) to diffuse into a concentrated solution of the material to be crystallized, and succeeded where all other attempts at crystallization had failed. Selective removal of the enolester function by mild treatment with potassium permanganate, together with the separation of the iodo-enolester intermediates, allowed the specific syntheses of a number of deoxy and unsaturated nucleosides. Among these are: 3'-deoxyadenosine (cordycepin), 6-amino-9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)purine (3',4'-unsaturated adenosine), 6-amino-9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-purine (2',3'-unsaturated adenosine), and the only reported synthesis of 6-amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)purine (1',2'-unsaturated adenosine). Since these transformations were carried out quite selectively, and on the individual isomers rather than mixtures, no complex separations were required to obtain the desired products in high yields. Hydrogenation of 3',4'-unsaturated adenosine to give 3'-deoxyadenosine and 6-amino-9-(3-deoxy-α-L-*threo*-pentofuranosyl)purine (the 4'-epimer of 3'-deoxyadenosine) as well as hydrogenation of 1',2'-unsaturated adenosine to give 2'-deoxyadenosine and 6-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine (the α-anomer of 2'-deoxyadenosine) were studied. Some furyl derivatives were also prepared and 9-(5-hydroxymethyl-2-furanyl)purine, obtained from deblocking of the furyl derivative mentioned above, was hydrogenated to racemic 2',3'-dideoxyadenosine.

Application of this route to certain tubercidin derivatives has also been made. In this case reaction of 2',3'-O-methoxyethylidenetubercidin with pivalyl chloride sodium iodide pyridine gave only the 3'-iodo-3'-deoxy-2'-O-enolester derivative. Analogous synthesis of 3',4'-unsaturated tubercidin and its hydrogenation to 3'-deoxytubercidin and its 4'-epimer was effected. Preparation of the analogous furyl derivatives and hydrogenation to racemic 2',3'-dideoxytubercidin have been performed.

All necessary chromatographic separations utilized in the course of this work employed columns, thus making them amenable to larger scale syntheses. The use of preparative thin layer chromatography was restricted to certain preliminary investigations.

ACKNOWLEDGMENTS

The criticisms and suggestions of my fellow students, together with the stimulation and rigorous experimental approach provided by Dr. Rudolph Mengel have been invaluable. I am particularly indebted to Professor Robins for his continuing support and guidance through the course of this work.

TABLE OF CONTENTS

Page

6

INTRODUCTION

A. A SELECTIVE HISTORY OF NUCLEOSIDES 1
B. A SURVEY OF PERTINENT NUCLEOSIDE SYNTHESES . . . 13
C. SOME RELEVANT PROPERTIES OF ACYLOXONIUM IONS . . . 35

DISCUSSION

A. REACTIONS OF 2',3'-O-METHOXYETHYLIDENE-ADENOSINE WITH PIVALYL HALIDE. 49
B. SPECIFIC SYNTHESES OF SOME DEOXY AND UNSATURATED ADENOSINE AND TUBERCIDIN DERIVATIVES 72
C. SOME REPRESENTATIVE NMR AND MASS SPECTRA 93

EXPERIMENTAL 7

A. GENERAL PROCEDURES 131
B. SYNTHESES. 134

REFERENCES. 181

LIST OF SCHEMES

Scheme	Description	Page
I	Proof of the Anomeric Configuration of Adenosine (1).	3
II	Purine (12) N^3,5'- and Pyrimidine (14) O^2,5'-Cyclonucleosides.	4
III	Bentley's Structure (15) for Cordycepin.	5
IV	Psicofuranine (21) and Decoyinine (22).	11
V	Goodman's Synthesis of 2'- and 3'-Deoxyadenosine (5 and 18).	16
VI	Synthesis of 2',3'-Dideoxyadenosine (20).	17
VII	Formation of the Adenosine S^8,2'-Cyclonucleoside (39).	18
VIII	Possible Mechanistic Route for the Formation of an O^2,2'-Cyclouridine (45) in the Reaction of 5'-O-Acetyl Uridine with Carbon Tetrachloride and Triphenylphosphine.	22
IX	Synthesis of 2',3'-Unsaturated Adenosine (46).	23
X	Formation of 2',3'-Unsaturated Uridine Derivatives (49 and 51).	24
XI	Synthesis of Decoyinine (22) from Psicofuranine (21).	25
XII	Synthesis of Adenosine 3',4'-Unsaturated-5'-Aldehyde (58) and Carboxylic Acid Ester (60) Derivatives.	27
XIII	Synthesis of Some 2'-Deoxy-3',4'-Unsaturated Nucleosides (64).	28
XIV	Reaction of a 2',3'-O-Benzylideneuridine Derivative (65) with NBS.	29
XV	Possible Mechanism of the Reaction of a Purine Nucleoside (70) with an α-acetoxyisobutyryl Halide (71).	31

Scheme	Description	Page
XVI	Solvolysis of threo-2-Acetoxy-3-Bromobutane (79).	35
XVII	Formation and Reaction of 2-Ethoxy-1,3-Dioxolane (83).	36
XVIII	Formation of the 2-Methyl-(cis-4,5-Tetramethylene)-1,3-Dioxolan-2-Ylium Ion (89).	37
XIX	Some Reactions of the 2-Methyl-(cis-4,5-Tetramethylene)-1,3-Dioxolan-2-Ylium Ion (89).	38
XX	Formation of 3,4,6-Tri-O-Acetyl-2-O-Trichloroacetyl-β-D-glucopyranosyl Chloride (100).	40
XXI	Reaction of NBS With Methyl 2,3-O-Benzylidene-5-O-Methyl-β-D-Ribofuranose (104).	41
XXII	Routes to Acyloxonium Ions from cis-1,2-Diols (107a,b,c, and d).	43
XXIII	Reaction of HBr in Acetic Acid with Cyclohexane-cis-1,2-Diol (113).	44
XXIV	A Use of the α-(Dimethylamino)Benzylidene Group.	46
XXV	Formation of trans-1-Chloro-2-O-Acetyl-Cyclohexane (122).	47
XXVI	Reaction of 2-Ethoxy-1,3-Dioxolane (124) with Acetyl Halides.	48
XXVII	Transformation of Penta-O-Acetyl-β-D-Glucopyranose (95) to an ido Derivative (130).	48
XXVIII	Reaction of 2',3'-O-Methoxyethylidene-adenosine (131) with Pivalyl Chloride.	53
XXIX	Reaction of Ketene Dimethylacetal (144) with Acyl Chlorides.	56
XXX	Reaction of the Adenosine Pivalylketene Acetal (138) with Methanol.	59

Scheme	Description	Page
XXXI	Preparation of Ethyl 4,4-Dimethyl-3-*O*-Pivaloxypent-2-Enoate.	64
XXXII	Preparation of 6-Amino-9-(3-deoxy-β-*D*-*glycero*-pent-3-enofuranosyl)purine (156).	77
XXXIII	Preparation of 6-Amino-9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)purine (46).	81
XXXIV	Preparation of 6-Amino-9-(2-deoxy-*D*-*erythro*-pent-1-enofuranosyl)purine (159).	86
XXXV	Preparation of Racemic 2',3'-Dideoxyadenosine (20 and 169).	88
XXXVI	Reactions of 2',3'-O-Methoxyethylidenetubercidin with Pivalyl Chloride and Sodium Iodide in Pyridine.	90
XXXVII	Fragmentation of Alkyl 4,4-Dimethyl-3-pivaloxypent-2-enoates.	100
XXXVIII	Conversion of ion *c* to ion *i*.	111

LIST OF FIGURES

Figure	Description	Page
1.	Nmr Spectrum of 6-N-Pivalamido-9-(3-chloro-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)purine (141) ($CDCl_3$).	52
2.	Nmr Spectrum of 6-N-Pivalamido-9-(3-chloro-3-deoxy-2-O-acetyl-5-O-pivalyl-β-D-xylofuranosyl)purine (134) ($CDCl_3$).	52
3.	Graph of Yield versus Reaction Time for Reaction of 2',3'-O-Methoxyethylideneadenosine (131) with Pivalyl Chloride and Sodium Iodide in Pyridine.	69
4.	Nmr Spectrum of 6-N-Pivalamido-9-(3-iodo-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)purine (150) ($CDCl_3$).	94
5.	Nmr Spectrum of 6-N-Pivalamido-9-(2-iodo-2-deoxy-5-O-pivalyl-3-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-arabinofuranosyl)purine (151) ($CDCl_3$).	94
6.	Nmr Spectrum of 6-N-Pivalamido-9-(3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-erythro-pentofuranosyl)purine (155) ($CDCl_3$).	95
7.	Nmr Spectrum of 6-N-Pivalamido-9-(2-deoxy-5-O-pivalyl-3-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-erythro-pentofuranosyl)purine (182) ($CDCl_3$).	95
8.	Nmr Spectrum of 4-N-Pivalamido-7-(3-iodo-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine (171) ($CDCl_3$).	96
9.	Nmr Spectrum of Ethyl 4,4-Dimethyl-3-pivaloxypent-2-enoate (154) ($CDCl_3$).	96

Figure	Description	Page
10.	Nmr Spectrum of 6-N-Pivalamido-9-(2,3-O-[4,4-dimethyl-3-oxo-pent-1-enylidene]-5-O-pivalyl-β-D-ribofuranosyl)purine (138) ($CDCl_3$).	97
11.	Mass Spectrum of Ethyl 4,4-Dimethyl-3-pivaloxypent-2-enoate (154).	99
12.	Mass Spectrum of Methyl 4,4-Dimethyl-3-pivaloxypent-2-enoate.	99
13.	Mass Spectrum of 6-N-Pivalamido-9-(3-chloro-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)purine (141).	102
14.	Mass Spectrum of 6-N-Pivalamido-9-(3-chloro-3-deoxy-2-O-acetyl-5-O-pivalyl-β-D-xylofuranosyl)purine (134).	102
15.	Mass Spectrum of 6-N-Pivalamido-9-(3-iodo-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)purine (150).	105
16.	Mass Spectrum of 6-N-Pivalamido-9-(2-iodo-2-deoxy-5-O-pivalyl-3-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-arabinofuranosyl)purine (151).	106
17.	Mass Spectrum of 6-N-Pivalamido-9-(3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-erythro-pentofuranosyl)purine (155).	107
18.	Mass Spectrum of 6-N-Pivalamido-9-(2-deoxy-5-O-pivalyl-3-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-erythro-pentofuranosyl)purine (182).	108
19.	Mass Spectrum of 6-N-Pivalamido-9-(3-iodo-3-deoxy-5-O-pivalyl-β-D-xylofuranosyl)purine (161).	109
20.	Mass Spectrum of 6-N-Pivalamido-9-(2-iodo-2-deoxy-5-O-pivalyl-β-D-arabinofuranosyl)purine (164).	109

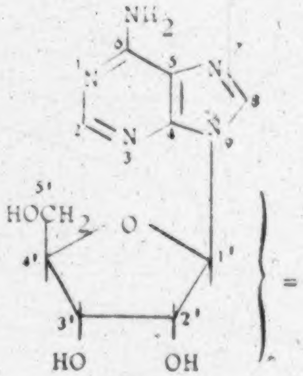
Figure	Description	Page
21.	Mass Spectrum of 4-*N*-Pivalamido-7-(3-iodo-3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-*D*-xylofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (171).	113
22.	Nmr Spectrum of 2'-Deoxyadenosine (5) (DMSO-d_6, D_2O).	114
23.	Nmr Spectrum of 6-Amino-9-(2-deoxy-α-*D*-*erythro*-pentofuranosyl)purine (167) (DMSO-d_6, D_2O).	114
24.	Nmr Spectrum of 3'-Deoxyadenosine (18) (DMSO-d_6, D_2O).	115
25.	Nmr Spectrum of 6-Amino-9-(3-deoxy-α-*L*-*threo*-pentofuranosyl)purine (61) (DMSO-d_6, D_2O).	115
26.	Nmr Spectrum of 3'-Deoxytubercidin (174) (DMSO-d_6, D_2O).	116
27.	Nmr Spectrum of 4-Amino-7-(3-deoxy-α-*L*-*threo*-pentofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (175) (DMSO-d_6, D_2O).	116
28.	Nmr Spectrum of Racemic 2',3'-Dideoxy-adenosine (20 and 169) (DMSO-d_6, D_2O).	118
29.	Nmr Spectrum of Racemic 2',3'-Dideoxy-tubercidin (178 and 179) (DMSO-d_6, D_2O).	118
30.	Nmr Spectrum of the Deoxy Protons of 2'-Deoxyadenosine (5) and 3'-Deoxyadenosine (18) (DMSO-d_6).	119
31.	Nmr Spectrum of 6-Amino-9-(3-deoxy-β-*D*-*glycero*-pent-3-enofuranosyl)purine (156). (DMSO-d_6).	121
32.	Nmr Spectrum of 4-Amino-7-(3-deoxy-β-*D*-*glycero*-pent-3-enofuranosyl)pyrrolo[2,3-*d*]pyrimidine (173). (DMSO-d_6).	121
33.	Nmr Spectrum of 6-Amino-9-(2-deoxy-*D*-*erythro*-pent-1-enofuranosyl)purine (159). (DMSO-d_6).	122

Figure	Description	Page
34.	Nmr Spectrum of 6-Amino-9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)purine (45). (DMSO-d_6).	123
35.	Mass Spectrum of 3'-Deoxytubercidin (174).	124
36.	Mass Spectrum of 4-Amino-7-(3-deoxy-α-L-threo-pentofuranosyl)pyrrolo[2,3-d]pyrimidine (175).	124
37.	Mass Spectrum of Racemic 2',3'-Dideoxyadenosine (20 and 169).	126
38.	Mass Spectrum of Racemic 2',3'-Dideoxytubercidin (171 and 179).	126
39.	Mass Spectrum of 6-N-Pivalamido-9-(5-O-pivalyl-D-erythro-pent-1-enofuranosyl)purine (166).	128
40.	Mass Spectrum of 6-N-Pivalamido-9-(5-pivaloxymethyl-2-furanyl)purine (153).	128
41.	Mass Spectrum of 6-N-Trimethylsilylamino-9-(2-deoxy-3,5-bis-O-trimethylsilyl-D-erythro-pent-1-enofuranosyl)purine.	129
42.	Mass Spectrum of 6-Amino-9-(3-deoxy-β-D-glycero-pent-3-enofuranosyl)purine (156).	130
43.	Mass Spectrum of 6-Amino-9-(5-hydroxymethyl-2-furanyl)purine (157).	130

INTRODUCTION

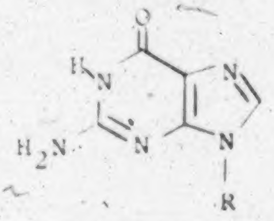
A. A SELECTIVE HISTORY OF NUCLEOSIDES

In 1909 the term "nucleoside" was first used by Levene and Jacobs[1] to describe the carbohydrate derivatives of purines and pyrimidines which had been isolated from alkaline hydrolysis of yeast nucleic acid. It has since been extended to include any carbohydrate or carbohydrate derivative linked through the C-1 carbon to a heterocyclic base, whether this is a C-N bond or a C-C bond. Nucleosides may nevertheless be conveniently divided into two general classes: those derived from nucleic acids; and those derived from other sources or obtained by chemical synthesis. The most common ribonucleic acid derived nucleosides are adenosine (1), guanosine (2), cytidine (3), and uridine (4). The nucleosides obtained from deoxyribonucleic acid are 2'-deoxyadenosine (5), 2'-deoxyguanosine (6), 2'-deoxycytidine (7), and thymidine (8).

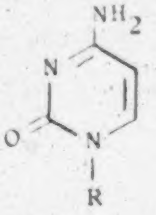


= R = D-ribose

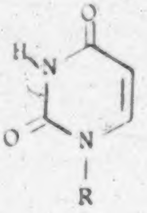
1
adenosine



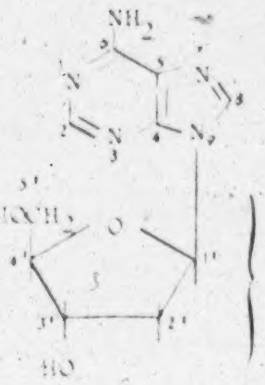
2
guanosine

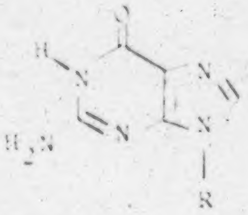


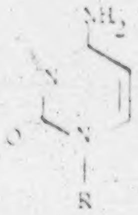
3
cytidine

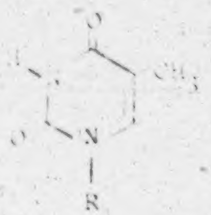


4
uridine









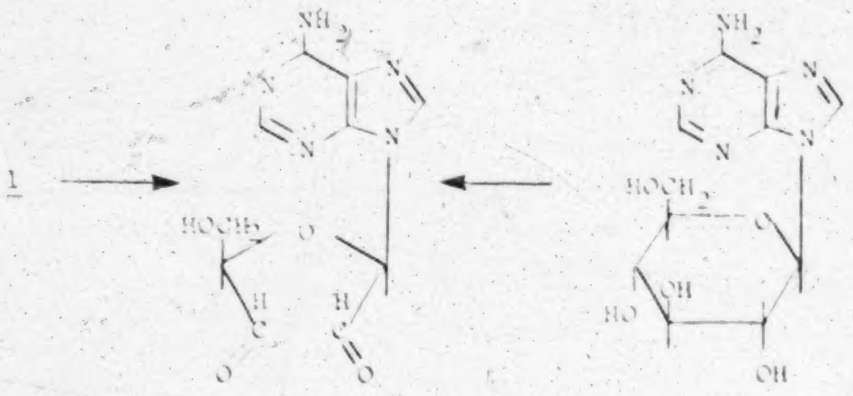
= R = 2-deoxy-D-*erythro*-pentose
(2-deoxy-D-ribose)

5 6, 7 8

2'-deoxyadenosine 2'-deoxyguanosine 2'-deoxycytidine thymidine

The five heterocyclic bases found in the common nucleosides had been identified in the late 19th century by Kossel, Schulze, and Fischer, among others.[2] However, the structures of the carbohydrate residues were not established until the years from 1910 to 1930 by Levene and coworkers.[3-5] In addition to these five bases, over thirty others have since been found to be present in nucleic acids in minor amounts. Most of the modified bases are simply methylated derivatives,[6] as is the only other nucleic acid derived sugar moiety, 2-O-methyl-D-ribose.[7] The determination of the point of attachment of the sugar on the base was first deduced by chemical methods,[8,9] but Gulland later showed that unequivocal assignment could be made simply by comparison of the ultraviolet spectrum with the spectra of specifically methylated bases.[10-12] Levene and Tipson demonstrated the furanose nature of the ribose ring by methylation, hydrolysis, and identification of the methylated sugar.[13]

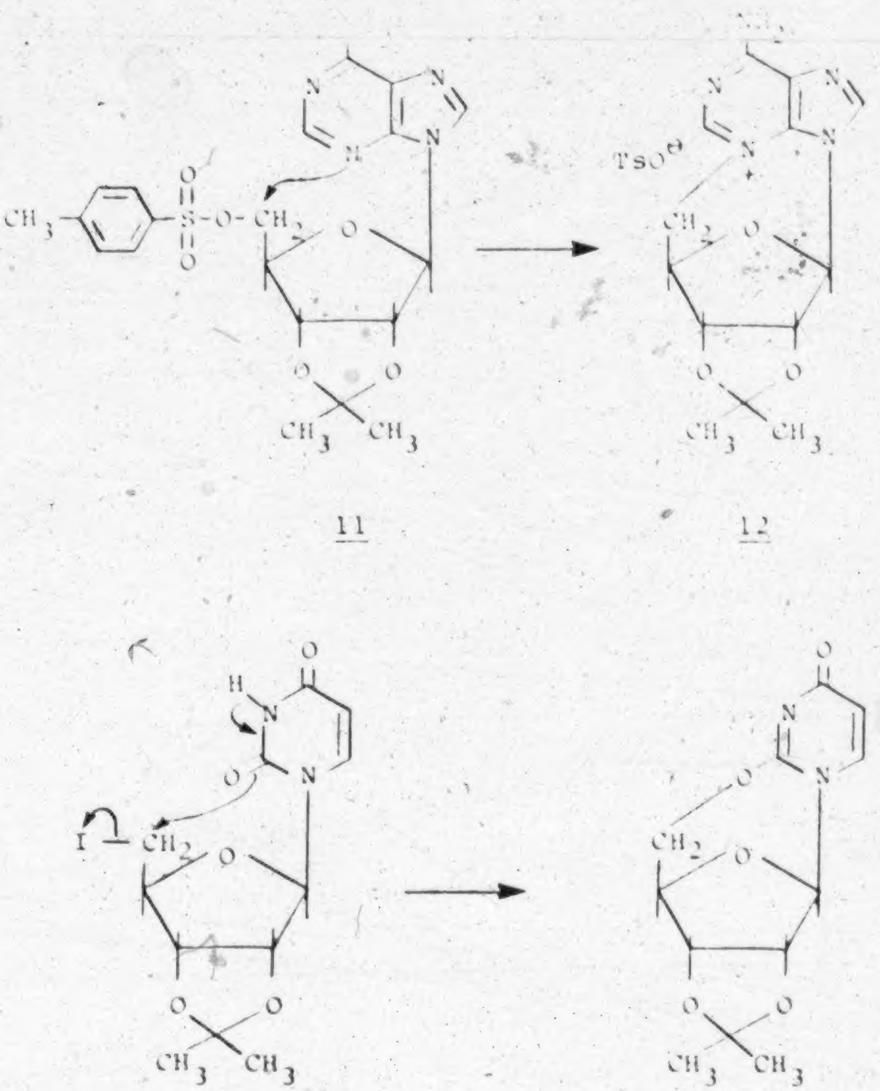
It was later found that oxidation by periodate led to the same conclusion, since a ribofuranosyl derivative will consume one mole of periodate while a ribopyranosyl derivative will consume two moles.[14,15] Todd and coworkers also used periodate oxidation to provide the first indication of configuration at the anomeric carbon. In this case adenosine (1) was converted to a dialdehyde (9) which was identical with the product obtained from periodate treatment of the β-glucoside 10.[16] The same group later



9 10

Scheme I

discovered the formation of cyclonucleosides via intramolecular displacement of a 5'-tosylate or iodide by the N^3 or O^2 of the base. As shown in Scheme II the formation of these cyclonucleosides is possible only for β anomers. The final structure proof, synthesis by an unambiguous route, has also been carried out by Todd and coworkers for all of the common nucleosides.[18] The foregoing material



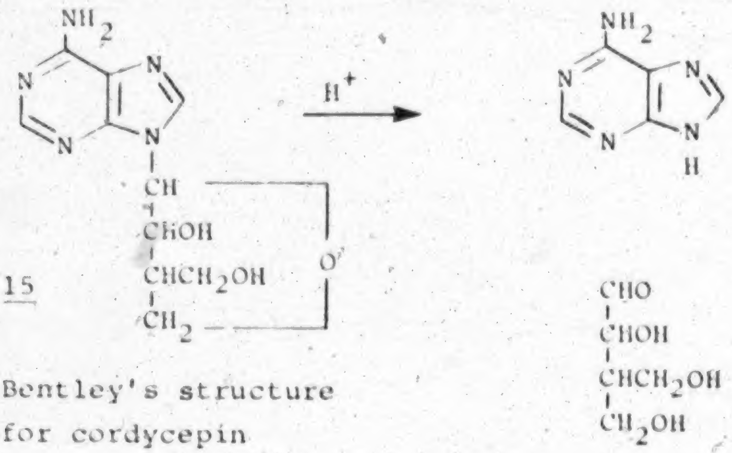
11 12

13 14

Scheme II

has been the subject of several extensive reviews.[19-23]

From the definition of "nucleoside" given above, it is clear that the structural diversity of these compounds is much greater than that observed in nucleic acids. However, because of the fundamental role of nucleic acids in all life processes, the most useful and interesting nucleosides have been those bearing a close structural relationship to the nucleic acid components. A number of nucleosides have been isolated as antibiotics, such as cordycepin, or synthesized and found to possess "antibiotic properties," such as 2',3'-dideoxyadenosine.[24,25] For the purpose of this discussion an "antibiotic" may be defined as a compound of microbial origin that is able to disrupt the normal metabolic functioning of other cells.[26] Cordycepin was the first of the nucleoside antibiotics to be discovered. It was isolated in 1951 by Cunningham from the mold Cordyceps militaris (Linn.) Link,[27] and was assigned structure 15 by Bentley in the same year.[28] Bentley had isolated adenine (16) after acid hydrolysis and had shown by ultraviolet spectroscopy that substitution was at the N-9 position. The nucleoside was found not to be oxidized



15

Bentley's structure for cordycepin

adenine

16

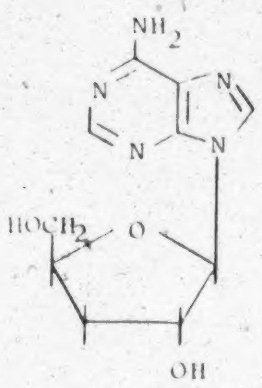
cordycepose

17

Scheme III

by periodate, but the sugar did readily form osazone derivatives, indicating the presence of a 2-hydroxyl group. Analysis of the osazones indicated a molecular formula of $C_5H_{10}O_4$ for the original sugar moiety and Bentley's conclusion was that the compound contained a 3-deoxypentose. Bentley next prepared the acid phenylhydrazide, m.p. 151, $[\alpha]_D$ +26°, by oxidation of the sugar with bromine water followed by reaction with phenylhydrazine. However, this product did not correspond in *both* melting point and optical rotation with any of the four possible phenylhydrazide derivatives of α,γ,δ-trihydroxyvaleric acid. One pair of these stereoisomers has a reported melting point of 150° but an optical rotation of only ±9°, and the other a rotation of ±26° but a melting point of only 110°.[29] Bentley therefore decided on the branched chain 3-deoxypentose 17. This structure was strongly supported four years later by the total synthesis of racemic 17 (cordyceose) by Raphael and Roxburgh.[30] The synthetic cordyceose (17) and the sugar derived from the antibiotic cordycepin were held to be identical in that their osazones had the same melting point, and a mixed melting point did not show depression.

Although this structure passed unchallenged until 1964, it has been shown to be incorrect. Cordycepin is actually 3'-deoxyadenosine (18). This was discovered by Folkers and coworkers, who in 1964 isolated a nucleoside from a fermentation of *Aspergillus nidulans* which they



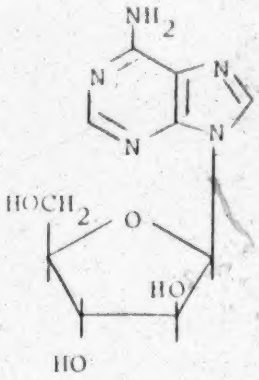
3'-deoxyadenosine
(cordycepin)

18

found to have identical infrared and nmr spectra with a sample of synthetic 3'-deoxyadenosine.[31] The identity of cordycepin from the mold Cordyceps militaris with 3'-deoxyadenosine was also established by the same physical methods.[32] The structure of the sugar of cordycepin has been further confirmed by Hanessian through comparison of the mass spectra of cordycepin and synthetic 3'-deoxyadenosine.[33]

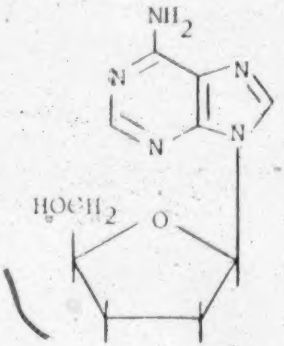
Not only has this misassignment of structure led to some confusion in nomenclature, but also to at least one erroneous conclusion. In 1963 Klenow found that monophosphorylated cordycepin was dephosphorylated by a snake venom 5'-nucleotidase at the same rate as was 2'-deoxyadenosine monophosphate, and concluded that the enzyme may be specific only for hydroxymethyl groups and not for the 5'-position.[34]

Arabinofuranosyladenine (9-β-D-arabinofuranosyladenine, spongoadenosine or ara-A) (19) is a nucleoside antibiotic whose chemical synthesis by Goodman and coworkers in 1960[35] preceded its isolation from a culture of *S. Antibioticus* by seven years.[36] Ara-A, together with cordycepin and the synthetic nucleoside 2',3'-dideoxyadenosine (20) have all been shown to interfere with



19

Ara-A



20

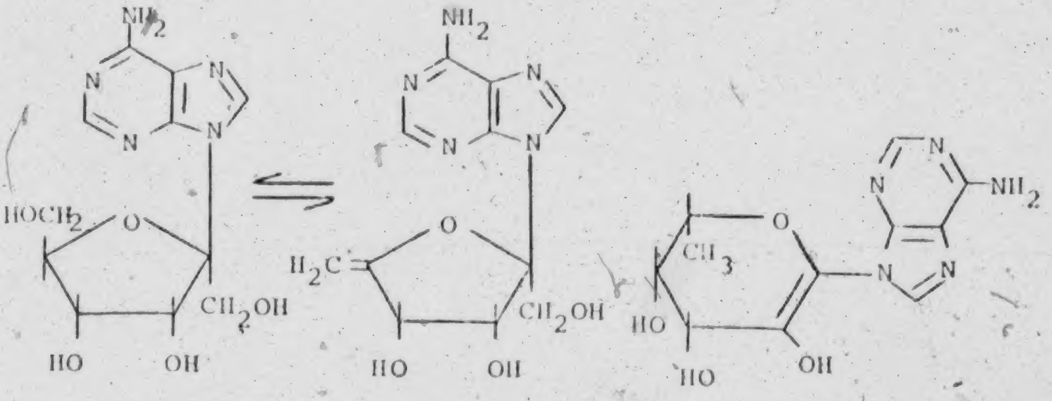
2',3'-dideoxyadenosine

the synthesis of either DNA or RNA, but not both. Thus, cordycepin strongly inhibits RNA synthesis but has no effect on DNA synthesis.[37] In experiments with RNA polymerase from *Micrococcus lysodeikticus*, Shigeura and Boxer observed the incorporation of the triphosphate of 3'-deoxyadenosine-^{14}C into RNA. Upon alkaline hydrolysis of this RNA, all of the radioactivity was contained in the nucleoside fraction, with essentially none in the nucleotide fraction.[38] This indicates that cordycepin was incorporated only at the terminal position, as alkaline hydrolysis of RNA proceeds via scission of the 5'-phosphate linkage, converting the terminal nucleotide to a nucleoside. Shigeura and Gordon demonstrated in 1965 that cordycepin was incorporated in place of adenosine. In studies on the formation of poly A and poly U catalyzed by RNA polymerase in the presence of DNA, poly A, or poly U, they found that only poly A formation was inhibited (94-98%).[39] From these results it is clear that 3'-deoxyadenosine, because of its structural relationship with adenosine, could be "recognized" as adenosine and incorporated into RNA, but that absence of a 3'-hydroxyl function prevented chain elongation. Cory *et al.* have reported the *in vitro* incorporation of cordycepin into an internucleotide link, but the amount was very small.[40]

Both 2',3'-dideoxyadenosine and ara-A act as 2'-deoxy analogs, since both inhibit DNA but not RNA synthesis.[37] Ara-A has been shown to be a chain terminator *in vitro* using a DNA polymerase from *E. coli*,[41,42] and DNA chain termination by **20** has been demonstrated by Cohen both *in vitro* and *in vivo* with *E. coli*.[24,25]

Recently Sprinzl and Cramer have prepared transfer ribonucleic acids (tRNAs) terminated in either 2'-deoxyadenosine or 3'-deoxyadenosine (cordycepin) and found that only the cordycepin-terminated tRNA was enzymatically aminoacylated.[43] In addition, they tested this aminoacylated 3'-deoxy tRNA in an *in vitro* peptide synthesizing system and found it to be without activity. On this basis Sprinzl and Cramer have suggested that tRNAs are "charged" on the 2'-hydroxyl, but that a transacylation to the 3'-hydroxyl must take place before the tRNA can participate in peptide synthesis. Robins et al. have recently synthesized aminoacylated 3'-deoxy and 2'-deoxyadenosines.[44] Preliminary biochemical testing has shown considerable bacterial inhibitory activity for some of these compounds, but the mechanistic implications are not yet clear. A very recent report by Chladek supports the results obtained by Sprinzl and Cramer. Chladek found that cytidylyl(3'-5')-2'-deoxy-3'-O-L-phenylalanyladenosine was an active acceptor in the peptidyl transferase reaction but the 3'-deoxy-2'-O-L-phenylalanyl isomer was completely inactive.[45]

The antibiotics psicofuranine (Angustmycin C) (21) and decoyinine (Angustmycin A) (22) exhibit a further structural divergence from the nucleic acid nucleosides. Although they produce interesting biochemical effects, it is perhaps not surprising that they are not incorporated into RNA or DNA. Yünsten et al. first isolated Angustmycin A and assigned it structure 23,[46-48] containing a 1',2'-double bond. This structural feature has not yet been observed in a naturally occurring nucleoside and the first 1',2'-unsaturated nucleoside was only recently synthesized in this laboratory.[49] The correct structure, 22, is based on nmr and chemical studies carried out by Hoeksema and coworkers in 1964.[50] The structures of both 21 and 22 have also been confirmed by total synthesis



21
psicofuranine

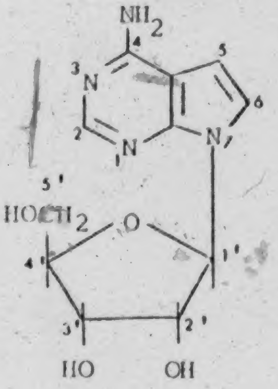
22
decoyinine

23
Yünsten's structure for
decoyinine
(Angustmycin A)

Scheme IV

and these syntheses will be discussed in the next section.

Finally, mention should be made of the class of nucleoside antibiotics derived from modification of the base rather than the sugar. Tubercidin (24) formally differs from adenosine only by replacement of the adenine N-7 with a C-H unit. Unlike the modified sugar analogs cordycepin and ara-A, which are only very poor substrates for adenosine kinase, tubercidin is readily phosphorylated by the enzyme.[51] In contrast, 24 is completely resistant to the action of adenosine deaminase which rapidly converts most modified adenine nucleosides to the inactive 6-one (hypoxanthine) derivatives.[52] In addition, it has been recently demonstrated that tubercidin triphosphate is capable of replacing adenosine triphosphate in RNA synthesis. This was shown using E. coli B RNA polymerase in one case and Mengovirus-induced RNA polymerase in another[53-55] The antibiotics discussed here, together



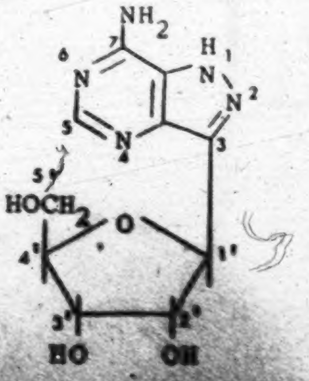
tubercidin

24

with a number of others, have been reviewed recently (1970) by Suhadolnik[37] and previously by Guarino (1967),[56] Suhadolnik (1967),[57] and Fox (1966).[26]

B. A SURVEY OF PERTINENT NUCLEOSIDE SYNTHESES

Syntheses of nucleosides containing modified sugars have been accomplished by three basic approaches. (1) The desired sugar may be synthesized separately and coupled with the appropriate heterocyclic base by a variety of techniques. (2) The heterocyclic base may be constructed from a suitable glycosyl-linked precursor of the desired sugar. (3) Transformations may be carried out on a nucleoside itself. All of these methods have been used and extensively reviewed.[20-23] The first two approaches involve coupling, or condensation, reactions which often give mixtures of α and β anomers. In addition, it has been found that the frequently used mercury salt coupling method can give products which are contaminated with minute amounts of mercuric ions. These trace ions are difficult to remove and may be biologically significant.[58-61] Other compounds, such as modified sugar analogs of the C-nucleoside formycin (24), are



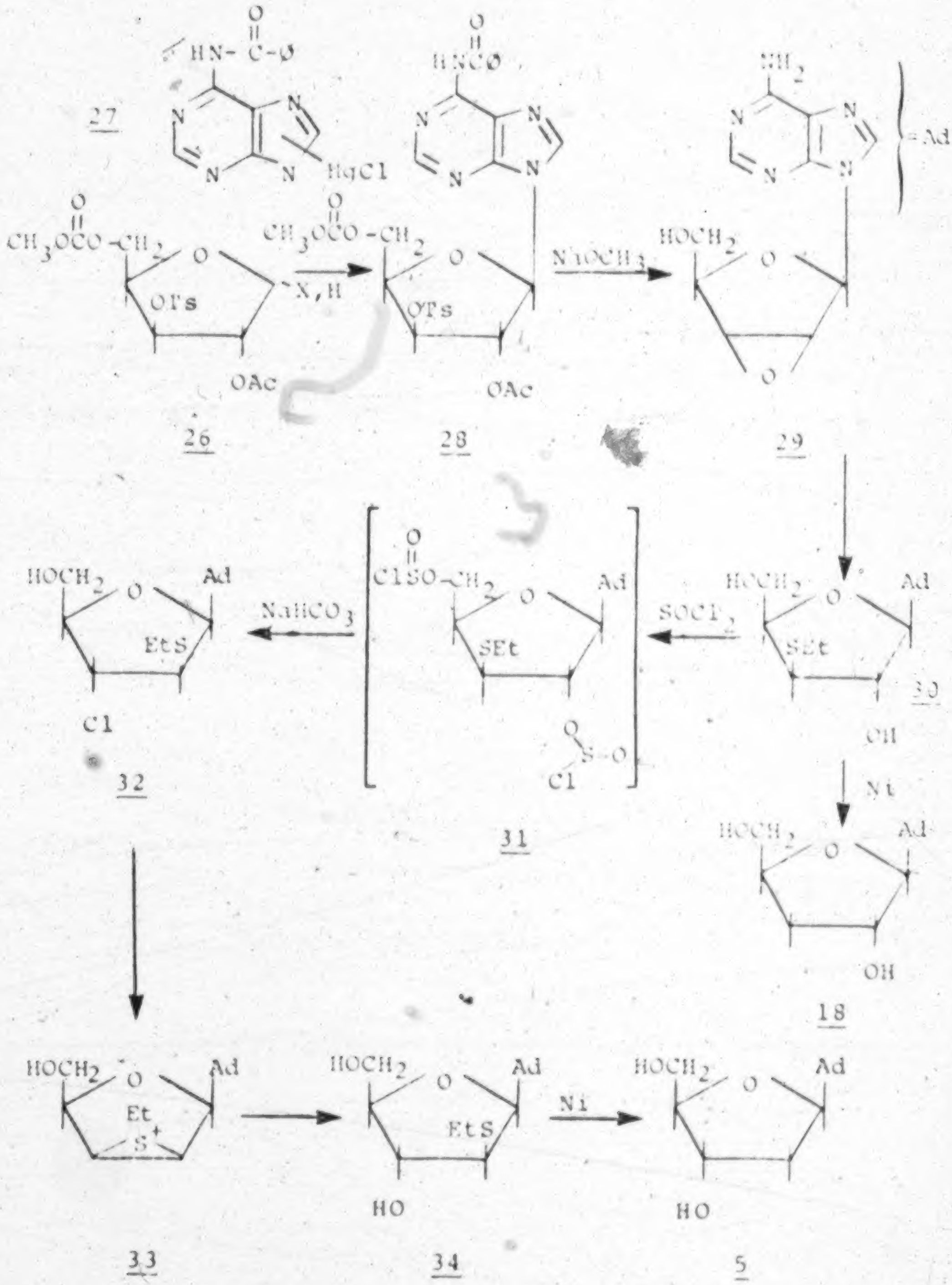
formycin

24

not amenable to direct synthesis by known coupling procedures. However, both formycin and tubercidin are available natural products for use as synthetic starting materials. For these reasons considerable effort has been expended in developing synthetic methods which are applicable to preformed nucleosides. Because the work to be discussed in this thesis deals specifically with the preparation of adenosine and tubercidin analogs containing deoxy or unsaturated sugars via transformation of the nucleoside to a halo derivative, only syntheses relevant to this approach will be reviewed in this section. In this regard little mention will be made of procedures used in pyrimidine nucleoside transformations. These almost invariably proceed with formation of an $\underline{O}^2$,-sugar cyclonucleoside which is subsequently opened by a halogen nucleophile or in a strong base catalyzed elimination. Purine $\underline{N}^3$,-sugar cyclonucleosides can be readily prepared, but suffer degradation of the purine ring and are thus of little synthetic value.

The first synthesis of 3'-deoxyadenosine was carried out by Todd and Ulbricht in 1960. This involved S_N2 displacement of the 3'-O-p-nitrobenzenesulfonyl derivative of adenosine with sodium iodide to give a 3'-iodo-3'-deoxy nucleoside which was hydrogenated to 3'-deoxyadenosine.[62] The authors mention that similar reactions attempted on 2'-O-p-nitrobenzenesulfonyladenosine failed.

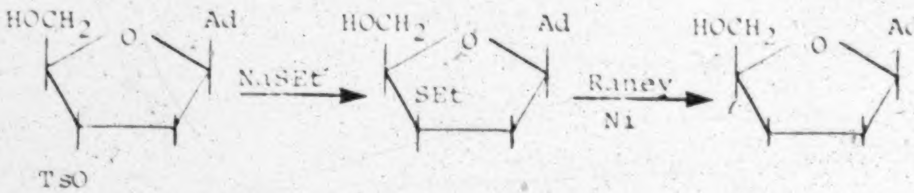
This lack of reactivity at the 2'-position had been exploited by Goodman and coworkers in a synthesis of 2'-deoxyadenosine and later in a synthesis of 3'-deoxyadenosine. In these syntheses (Scheme V) the adenosine 2',3'-riboepoxide (29) was prepared by coupling of 26 with 6-benzamidopurine chloromercury salt (27) to give 28. Treatment of this product (28) with methoxide gave anhydro formation and concomitant deblocking. The resulting epoxide (29) was opened with sodium ethylmercaptide to give the 3'-S-ethyl-3'-deoxy xylofuranosyl nucleoside (30). This could be desulfurized directly to 3'-deoxyadenosine (18) or converted to the 3'-chloro-2'-S-ethyl-2',3'-dideoxyarabinofuranosyl derivative (32) by treatment with thionyl chloride followed by sodium bicarbonate. The latter reaction presumably proceeded through the 2',3'-episulfonium ion (33), which was opened at the 3'-position by chloride ion. Treatment of 32 with sodium acetate in 95% aqueous methyl cellosolve gave the episulfonium ion (33), which was again attacked mainly at the 3'-position by acetate. Desulfurization of the deblocked derivative (34) with Raney nickel gave 2'-deoxyadenosine (5). The overall yield of 5 was 0.5%.[35,63] The first synthesis of 2',3'-dideoxyadenosine (20) was also achieved by displacement of a 3'-O-tosylate. In this case 3'-O-tosyl-2'-deoxyadenosine (35) was reacted with sodium ethyl mercaptide to give 36 which was



27
HN-C-0
HgCl
CH3OCO-CH2
OTs
OAc
26
X,H
28
NaOCH3
29
= Ad
HOCH2
30
SOCl2
31
ClSO-CH2
SEt
Ad
NaHCO3
32
EtS
Cl
Ni
18
OH
33
Et
S+
34
HO
5

Scheme V

desulfurized to 20.[64]

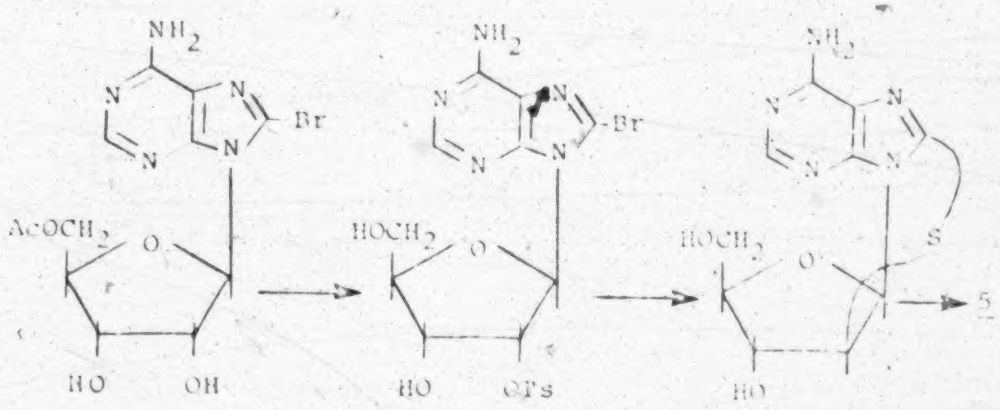


35 36 20

Scheme VI

The use of displacement reactions on the (primary) 5'-position has been complicated because of facile N^3,5'-cyclonucleoside formation. However, in 1965 Jahn found that acylation of the 6-amino group reduced the tendency for N-3 displacement at the 5'-position. Accordingly, Jahn was able to convert 5'-O-tosyladenosine into the corresponding 5'-iodo, bromo, chloro, azido, and amino 5'-deoxy derivatives by per-acylation followed by displacement with the appropriate nucleophile.[65] Similarly 2',3'-O-isopropylidene-5'-O-mesyltubercidin was first per-benzoylated and the 5'-O-mesyl then displaced with sodium iodide. Hydrogenation, followed by deblocking, gave 5'-deoxytubercidin.[66] The use of tetra-n-butyl ammonium fluoride to displace the 5'-O-tosyl of 2'-deoxyuridine and thymidine giving the corresponding 5'-fluoro-5'-deoxy compounds has also been reported.[67]

A type of purine cyclonucleoside which has been used in the formation of deoxy nucleosides of both adenosine and guanosine is the $\underline{S}^8$, 2'-, 3'-, or 5'-cyclonucleoside.[68-70] The $\underline{S}$-8 is nucleophilic enough to complete successfully with the $\underline{N}$-3 in cyclonucleoside formation. Scheme VII shows part of a reaction sequence by which Ikehara and Tada prepared 2'-deoxyadenosine (5) and 3'-deoxyadenosine (18). Tosylation of 5'-$\underline{O}$-Acetyl-8-bromoadenosine (37) gave a mixture of the 2'- (38), 3'-, and 2',3'-di-$\underline{O}$-tosylates in a ratio of 3:1:1. Treatment with thiourea gave the $\underline{S}^8$,2'- (39) or $\underline{S}^8$,3'-cyclonucleoside which could then be desulfurized to give 5 or 18, respectively. The ditosylate gave only the product of displacement of the 2'-$\underline{O}$-tosyl and a similar reaction sequence with the dimesylate favored 2'-displacement by a ratio of about 3:1. This regioselectivity is thought to be the result of steric strain involved in formation of the

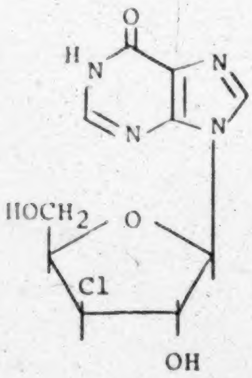


37 38 39

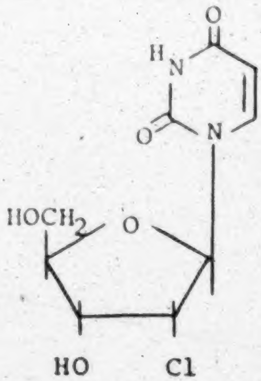
Scheme VII

$\underline{S}^8$,3'-cyclonucleoside. A recent review of purine-8-cyclonucleosides by Ikehara is available.[71]

Perhaps the best method of preparing 5'-iodo-5'-deoxy pyrimidine nucleosides is by treatment of the 2',3'-$\underline{O}$-isopropylidene derivative with methyltriphenoxyphosphonium iodide, a procedure reported by Verheyden and Moffatt in 1970.[72] Unfortunately, with purine nucleosides the major or exclusive product is the $\underline{N}^3$,5'-cyclonucleoside as would be expected from the known facile formation of these compounds. Attempted application of this reagent to the iodination of pyrimidine nucleoside secondary hydroxyls was successful only with thymidine, where there is no cis vicinal hydroxyl group.[73] Another method for the preparation of 5'-halo-5'-deoxy compounds, in this case the chloro and bromo derivatives of adenosine, cytidine, and uridine, is the use of Vilsmeir-Haack type complexes derived from the appropriate thionyl halide and dimethylformamide (DMF) or hexamethylphosphoramide (HMPA).[74,75] This reagent has also been used in the formation of the cytidine $\underline{O}^2$,2'-cyclonucleoside.[76] An apparently more versatile procedure is the use of triphenylphosphine and a halogen source such as carbon tetrachloride, carbon tetrabromide, carbon tetraiodide, bromine, cyanogen bromide, $\underline{N}$-bromosuccinimide (NBS), or iodine. This general procedure has been applied to the halogenation of both primary and secondary hydroxyl groups of nucleosides. The reaction of NBS and triphenylphosphine with 2',3'-O-benzylideneuridine gives the 5'-bromo-5'-deoxy derivative.[77] In the absence of triphenylphosphine the NBS reaction takes a very different course, as will be discussed later. The 5'-chloro, bromo, and iodo-5'-deoxy-2',3'-O-isopropylidene inosine derivatives have been prepared from 2',3'-O-isopropylidene inosine by reaction with triphenylphosphine and an appropriate halogen source.[78] In addition, the same authors report formation of 9-(3-chloro-3-deoxy-β-D-xylofuranosyl)hypoxyanthine (40) in 19% yield from the 5'-O-acetyl compound, with no trace of the 2'-isomer detected. Using this same reagent, Verheyden and Moffatt have prepared 5'-chloro-5'-deoxyadenosine as well as some 5'-halo-5'-deoxypyrimidine nucleosides.[79] They also reported that reaction of 5'-O-acetyluridine with triphenylphosphine and carbon tetrachloride gave a 38% yield of the 2'-chloro-2'-deoxy-5'-O-acetylribofuranosyl derivative (41), with none of the 3'-isomer found. The



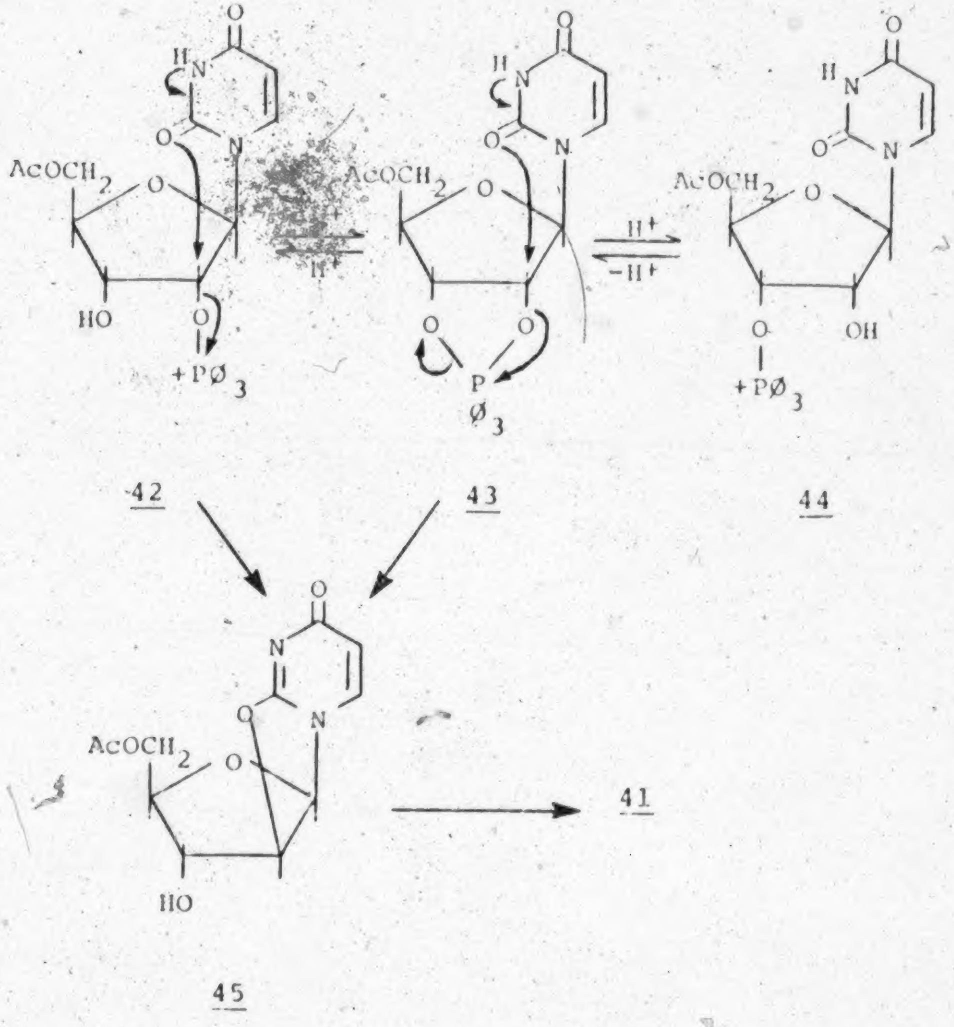
40



41

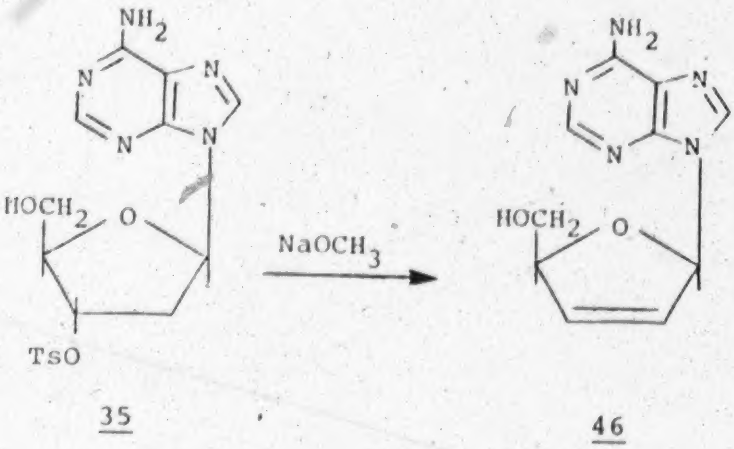
product is that of overall retention of configuration due to double inversion involving intermediate $\underline{O}^2$,2'-cyclonucleoside formation, as is normally the case with pyrimidine nucleosides. The authors[79] explain the specific formation of the 2'-isomer as the result of a greater reactivity of the 2'-hydroxyl, evidenced in such reactions as tosylation and diazomethane methylation. However, this does not seem to be consistent with the results obtained in the reaction of inosine, mentioned above, which gave the 3'-isomer. Since it is well known that $\underline{O}^2$,2'-cyclouridines are much more easily formed than the $\underline{O}^2$,3'-cyclouridines,[23] it seems more likely that the intermediate triphenylphosphonium ion gives an equilibrium mixture of interconvertible isomers (Scheme VIII) and that the position of attack by the 2-carbonyl is a result of known specificity based on the steric constraints of cyclonucleoside formation.

Tosylates and mesylates, as well as being used for displacement, have also served to introduce unsaturation directly through elimination with bases such as sodium methoxide or potassium $\underline{t}$-butoxide.[80] The first syntheses of 2',3'-dideoxy-2',3'-didehydroadenosine (46) were effected by the sodium methoxide or ethoxide catalyzed elimination of toluenesulfonic acid from 3'-$\underline{O}$-tosyl-2'-deoxyadenosine (35).[81,82]



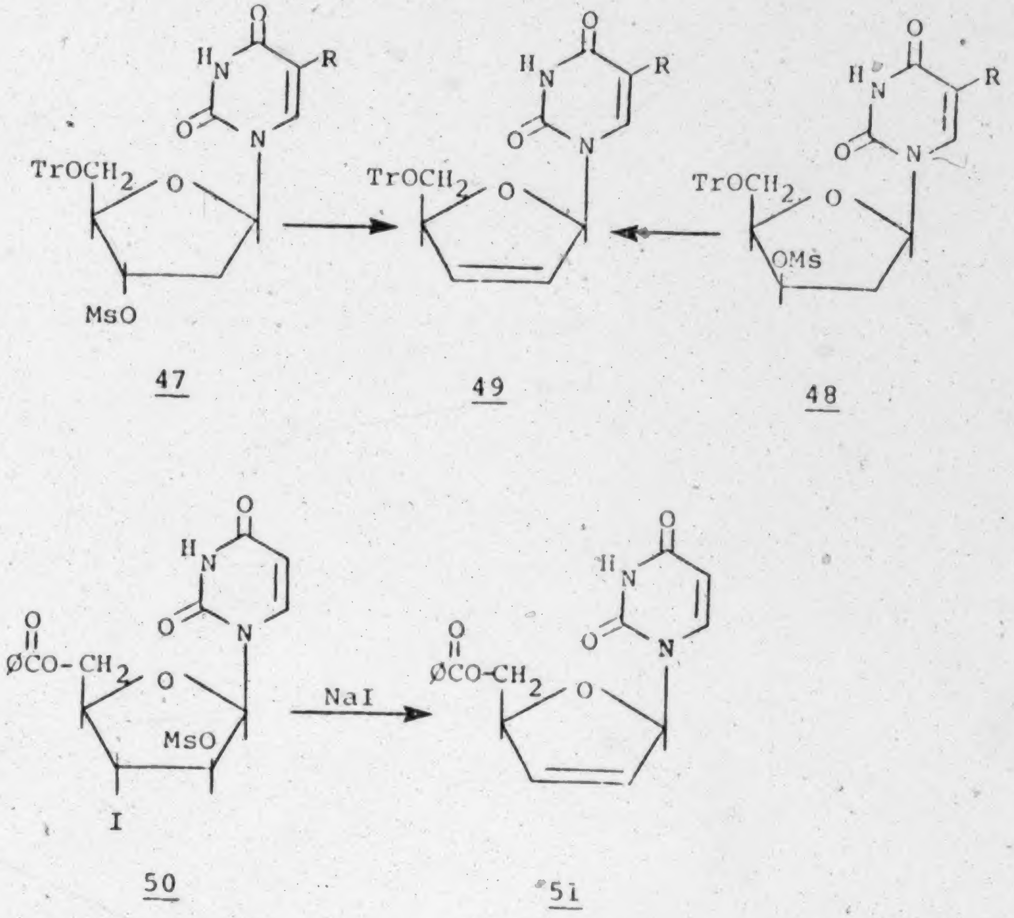
Scheme VIII

Horwitz has reported that the 3'-O-mesyl function is readily eliminated from both ribo (47) and xylo (48) configurations of thymidine and 2'-deoxyuridine derivatives giving the corresponding 2',3'-unsaturated compounds (49).[83] The same product was also obtained from the O^2,3'-cyclonucleoside, and analogous treatment of 3',5'-anhydro-2'-deoxyuridine gave 2',3'-unsaturation as well. It was also reported that (51) could be obtained by mild treatment of a 3'-iodo-2'-O-mesyl derivative (50) with sodium iodide in acetone.



Scheme IX

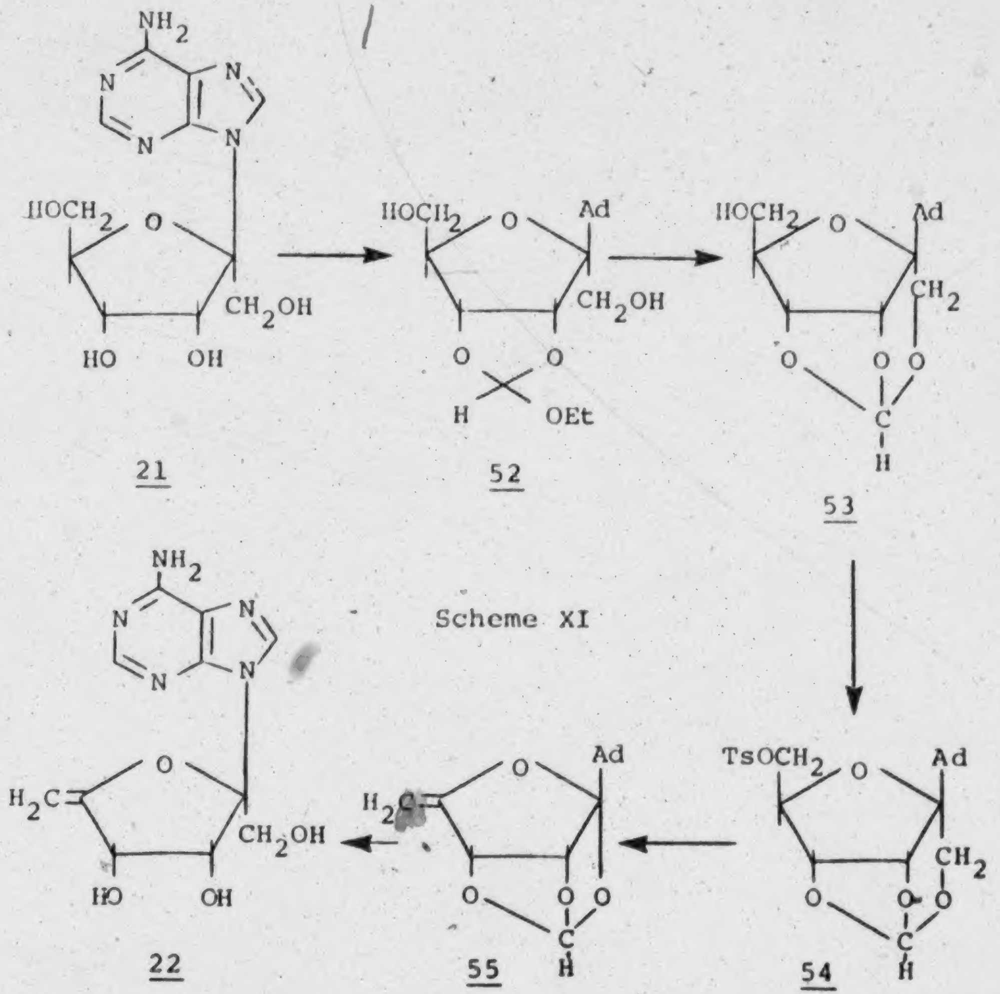
The 2',3'-unsaturated thymidine nucleotide was inadvertently prepared in an attempted phosphorylation of 3'-iodo-3'-deoxy thymidine.[84] A xylo 3',5'-cyclic-phosphate was apparently formed and then eliminated to give this product. Recently a 2',3'-di-O-mesyl-tubercidin derivative has been used to prepare 2',3'-unsaturated tubercidin derivatives by treatment with zinc and sodium iodide.[85] Inexplicably, the mono and dibenzoylated products of these transformations were not deblocked to the free nucleoside. These authors attempted



Scheme X

to use the Corey-Winter[86] olefin synthesis employing a 2',3'-O-thionocarbonate compound, but with little success. A 2',3'-unsaturated uridine derivative has been prepared in low yield by a modification of this procedure using deactivated Raney nickel on the corresponding 2',3'-O-thionocarbonate.[87]

McCarthy et al. later used elimination of toluenesulfonic acid from a 6'-O-tosyl derivative in a synthesis of the antibiotic decoyinine (22).[88] A key feature of the latter synthesis is the selective blocking of the primary C1'-hydroxyl group while leaving the other primary hydroxyl at C6' free for tosylation and subsequent elimination. This was accomplished by preparing the 3',4'-O-ethoxymethylidine derivative (52) of psicofuranine (21)

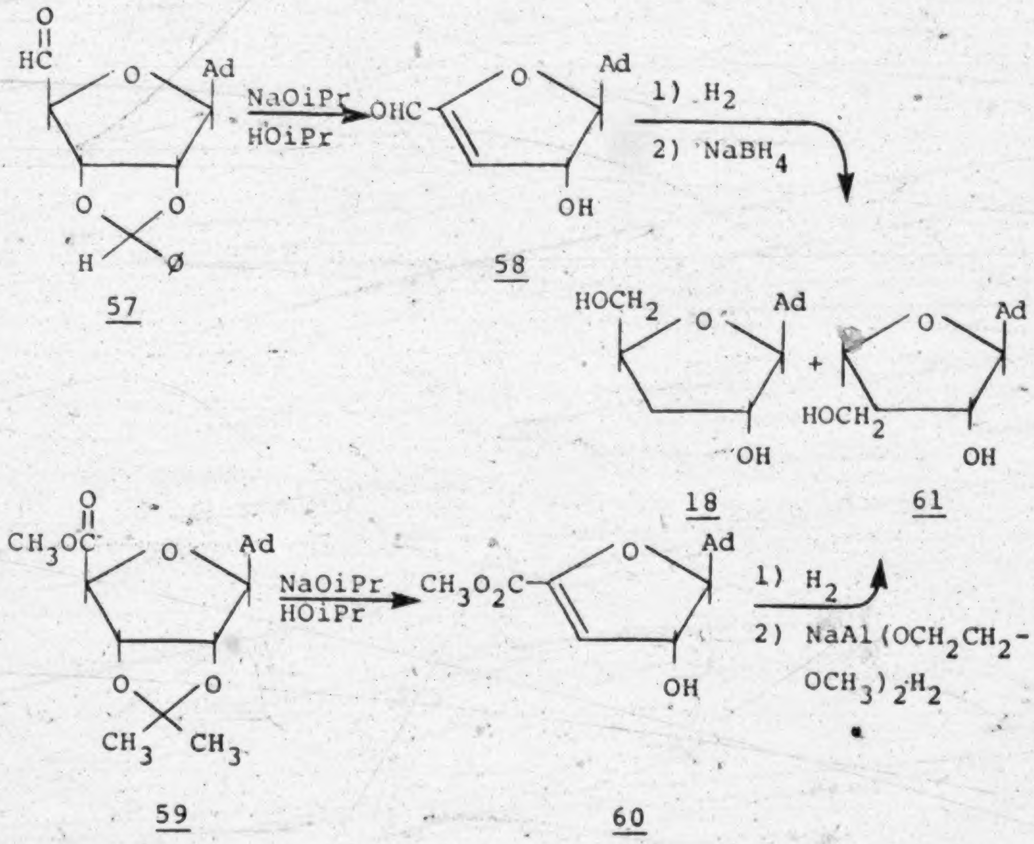


Scheme XI

and then using borontrifluoride etherate to effect ring closure to 53, leaving only the C6'-hydroxyl free.

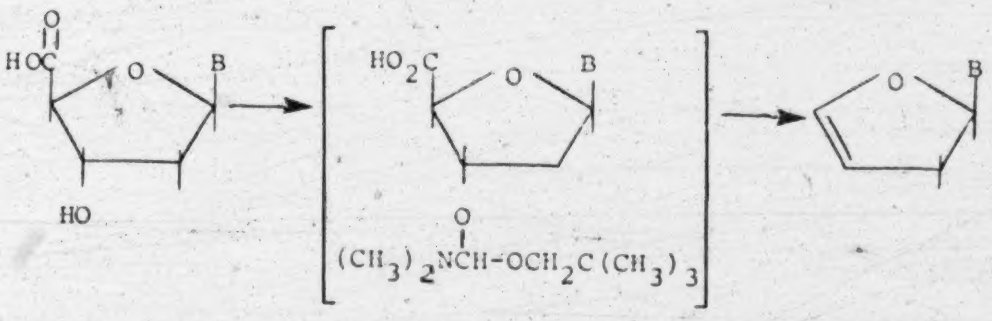
An early step in synthesis of the antibiotic nucleocidin by Jenkins et al. involved the t-butoxide catalyzed elimination of methanesulfonic acid from 5'-O-mesyl-2',3'-O-isopropylidene-6-N-benzoyladenosine giving the 4',5'-unsaturated derivative.[89] Introduction of 4',5'-unsaturation into uridine had earlier been accomplished by silver fluoride induced elimination of hydrogen iodide from a 5'-iodo-5'-deoxy deriv[illegible][90] and by the t-butoxide catalyzed elimination of toluenesulfonic acid from 5'-O-tosyl uridine.[91]

Certain 3',4'-unsaturated nucleosides have also been prepared by direct elimination. The earliest method involved treatment of 2',3'-O-alkylidene-5'-aldehyde derivatives with a variety of bases.[92,93] For example, reaction of (57) with sodium isopropoxide gave 6-amino-9-(5-aldehydo-3-deoxy-β-D-glycero-pent-3-enofuranosyl)-purine (58).[92] A similar process using the methyl ester of 2',3'-O-isopropylidene-adenosine-5'-carboxylic acid (59) in a sodium isopropoxide catalyzed elimination gave the corresponding 3',4'-unsaturated derivative (60).[94] As with the 5'-aldehyde, this was converted to a mixture of 3'-deoxyadenosine (18) and its α-L-anomer (61) by hydrogenation of the double bond followed by reduction of the aldehyde or ester functions. Zemlicka and Horwitz



Scheme XII

extended this type of elimination to 2'-deoxynucleosides using a 3'-O-mesyl as leaving group in conjunction with a 5'-carboxylic acid ester to activate the 4'-proton.[95] These workers had earlier found that treatment of a 2'-deoxy-nucleoside-5'-carboxylic acid (62) with dimethylformamide dineopentyl acetal gave "decarboxylative-elimination" to (64), presumably via (63).[96] The production of both 2',3'- and 3',4'-unsaturated derivatives



62 63 64

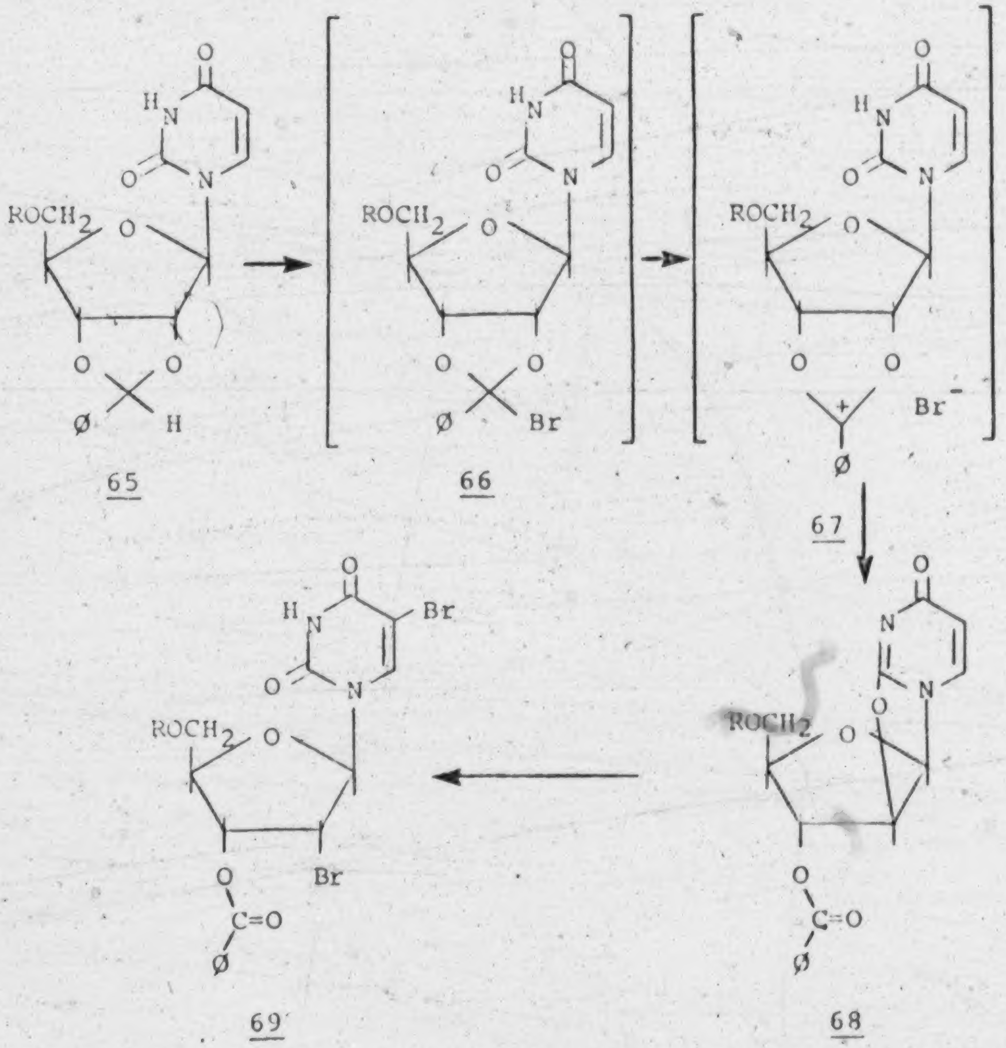
B = thymine, uracil, 5-fluorouracil, adenine

Scheme XIII

from 5'-fluoro-5'-deoxy-3'-O-mesylthymidine upon treatment with potassium t-butoxide has also been reported.[97]

Very recently several new approaches to the synthesis of 2'- (3'-) halo-2'-(3'-)deoxy nucleosides involving the intermediacy of 2',3'-acyloxonium ions have been developed. Hanessian and coworkers have studied the reaction of N-bromosuccinimide (NBS) with O-benzylidene acetals of a number of carbohydrates[98-100] and more recently some pyrimidine 2',3'-O-benzylidene derivatives.[101,102] The reaction of NBS with 2',3'-O-benzylidene uridine (65) gave exclusively 5,2'-dibromo-2'-deoxy-3'-O-benzoyl uridine (69). Similar treatment of 5'-O-acetyl-2',3'-O-benzylidene uridine gave O^2,2'-

cyclouridine (68). The mechanism of the reaction of NBS with benzylidene acetals is thought to proceed by a radical mechanism to an α-bromo acetal intermediate which then ionizes. The resulting benzoxonium ion is opened by an available nucleophile, in this case the 2-carbonyl. The cyclonucleoside may then react further to the 2'-bromo-2'-deoxy derivative. Concomitant bromination of the 5-position of the base does not present any difficulty

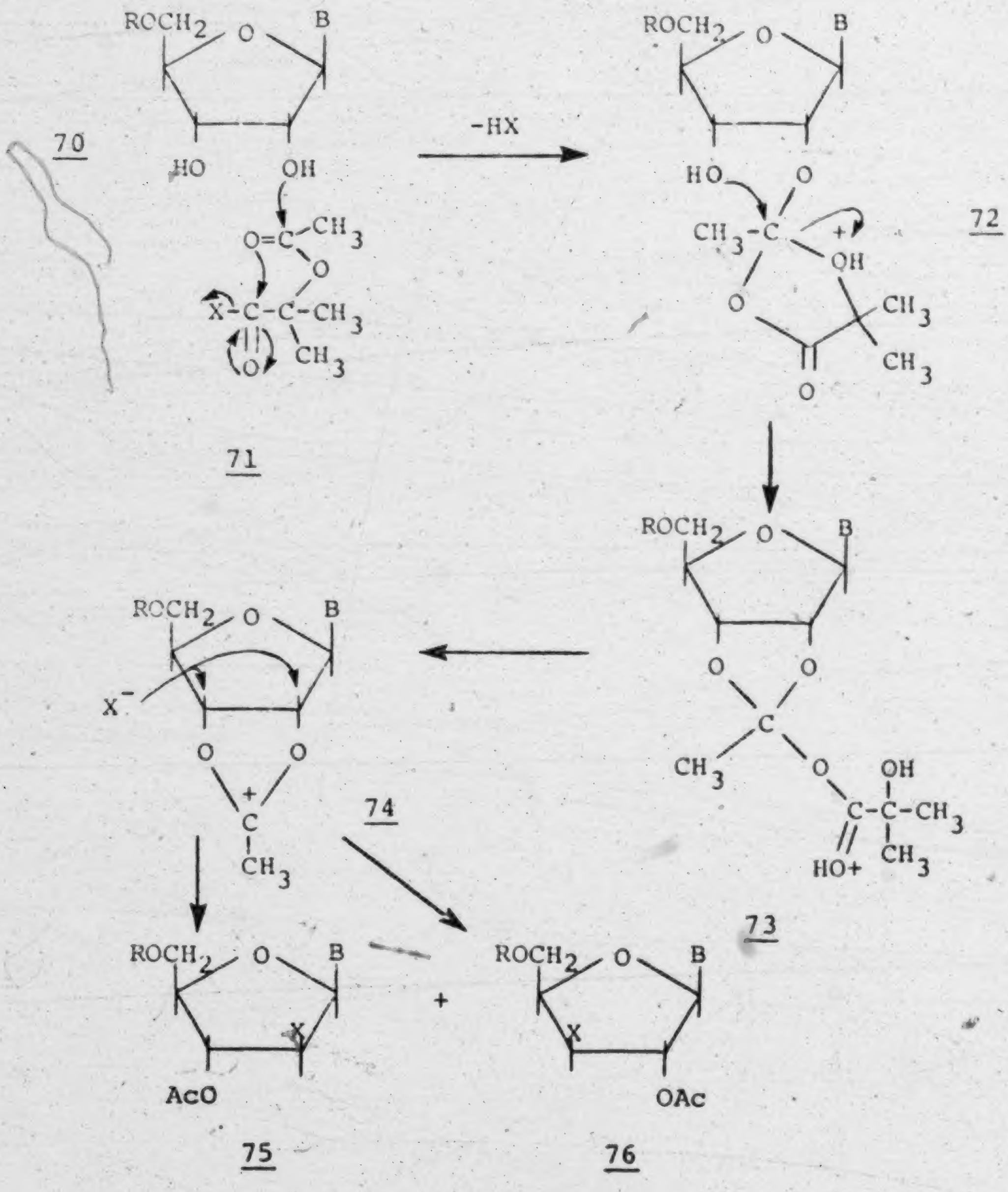


Scheme XIV

since 5-halogenated pyrimidines are themselves of biochemical interest and, if desired, the bromine is easily removed by hydrogenolysis.

Another approach which has been applied to the synthesis of purine nucleoside derivatives is the use of α-acetoxyisobutryl halides.[103] The general reaction was discovered by Mattocks in 1964 when he found that reaction of α-acyloxy acid chlorides with 1,2- and 1,3-diols gave 1,2 and 1,3 chloroacetates.[104,105] This approach, with subsequent hydrogenation, has been used in the synthesis of 3'-deoxytubercidin and 2'- and 3'-deoxyformycin.[106,107] In addition uridine and adenosine derivatives have been prepared,[108,109] and there have been preliminary reports of application to guanosine and inosine.[110] A plausible mechanism for the reaction is shown in Scheme XV.[106] Attack of either the 2'- or 3'-hydroxyl of 70 on the acetyl carbonyl carbon of a 2-acetoxyisobutyryl halide (71) would lead to a 2'- or 3'-O-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl) intermediate such as 72. Protonation of the ether oxygen of the dioxolan followed by attack of the cis hydroxyl gives the mixed orthoester anhydride 73. This intermediate could be protonated on the carbonyl oxygen and lose α-hydroxyisobutyric acid leading to the 2',3'-acetoxonium ion 74. The acetoxonium ion can then be attacked by an available nucleophile at either the 2'-or 3'-position giving the 2'-

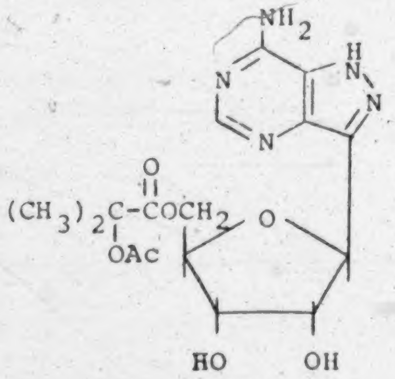
halo-2'-deoxy-3'-*O*-acetyl arabinofuranosyl compound [(75) or the 3'-halo-3'-deoxy-2'-*O*-acetyl-xylofuranosyl compound (76)]. Alternatively protonation of one of the ester oxygens of 72 can also be visualized as leading to 74 by analogous



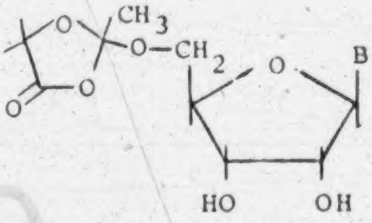
Scheme XV

transformations.[108] The position of nucleophilic opening of the acetoxonium ion produced has been shown to be dependent on the heterocyclic base present. Uridine, of course, is subject to exclusive 2'- opening due to participation of the 2-carbonyl. Both of the groups that have studied the reaction with tubercidin and formycin have found that while formycin gives a 3:2[106] or 3:1[107] ratio of 3'- to 2'- attack, tubercidin gives exclusively the product of opening at the 3'-position. Inosine, guanosine, and adenosine are all reported to give mixtures of isomers.[107,109] With adenosine, Moffatt and coworkers report that 3'- attack is favored by about 10:1, although they have not developed any practical separation of the isomers to verify this contention.[109] The products themselves constitute compelling evidence for the intermediacy of an acyloxonium ion, and a trapping experiment with sodium borohydride gave a 16% yield of the expected 2',3'-O-ethylidene product.[108]

The nature of the 5'-substituent produced in this reaction is variable and appears to be both solvent and base dependent. For example, the reaction of uridine in acetonitrile, DMF, ethyl acetate, dioxane, or butyrolactone gives mainly the 5'-O-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl) derivative (77), analogous to the formation of 72. However, in nitromethane or in the absence of solvent, reaction proceeds to the simple 5'-O-(α-acetoxyisobutyrate) ester (78). With the purine type nucleosides studied, only formycin appears to give the acetoxyisobutyrate (78), the dioxolane (77) being the exclusive product in reactions of adenosine, tubercidin, and inosine. No explanation of this phenomenon has been suggested.



78



77

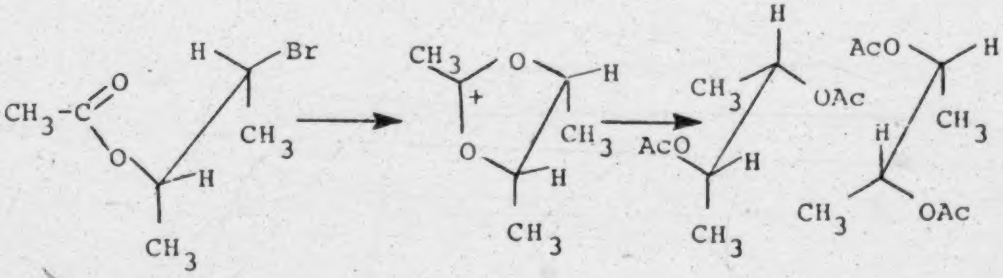
B = adenine-9;
hypoxanthine-9;
4-amino-pyrrolo-[2,3-d]-
pyrimidine-7

Very recently Moffatt and coworkers have also reported the conversion of some of the above halo nucleosides to the corresponding 2',3'- and 3',4'-unsaturated derivatives.[111] Treatment with chromous acetate gave conversion of the halo acetates to mixtures of the 2',3'-unsaturated, 3'-deoxy, and small amounts of the 3',4'-unsaturated nucleosides.

Yet a different approach to the synthesis of halo nucleosides involves conversion of 2',3'-orthoester derivatives to acyloxonium ions.[112-114] This approach forms the basis of this thesis and will be discussed in the following section, along with a detailed comparison with the procedures used by Moffatt *et al*.

C. SOME RELEVANT PROPERTIES OF ACYLOXONIUM IONS

The existence of acyloxonium ions, or more properly, 1,3-dioxolan-2-ylium ions, was first demonstrated by the work of Winstein and of Meerwein. Early examples came from Winstein's study of solvolysis reactions such as the conversion of *threo*-2-acetoxy-3-bromobutane (79) to D,L-2,3-diacetoxybutane (81) with silver acetate in dry acetic acid, in which the acyloxonium ion (80) is formed by neighboring group participation.[115] Meerwein had

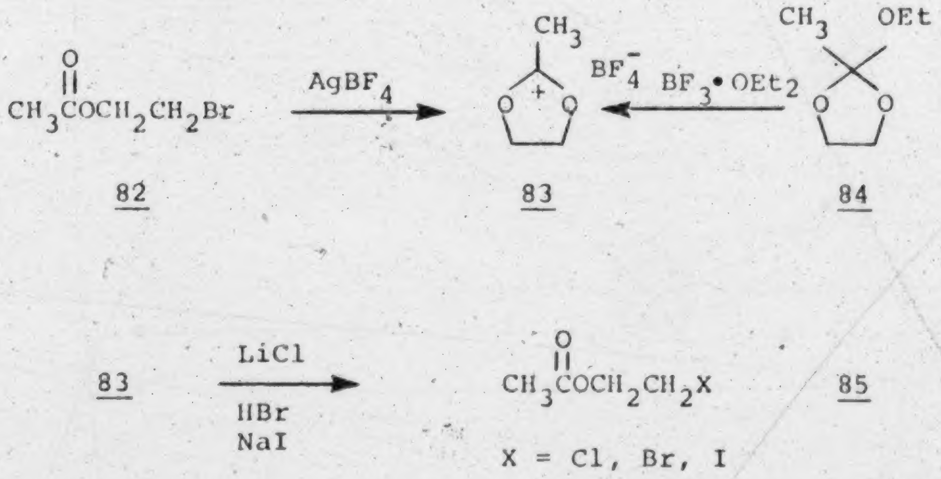


79 80 81

Scheme XVI

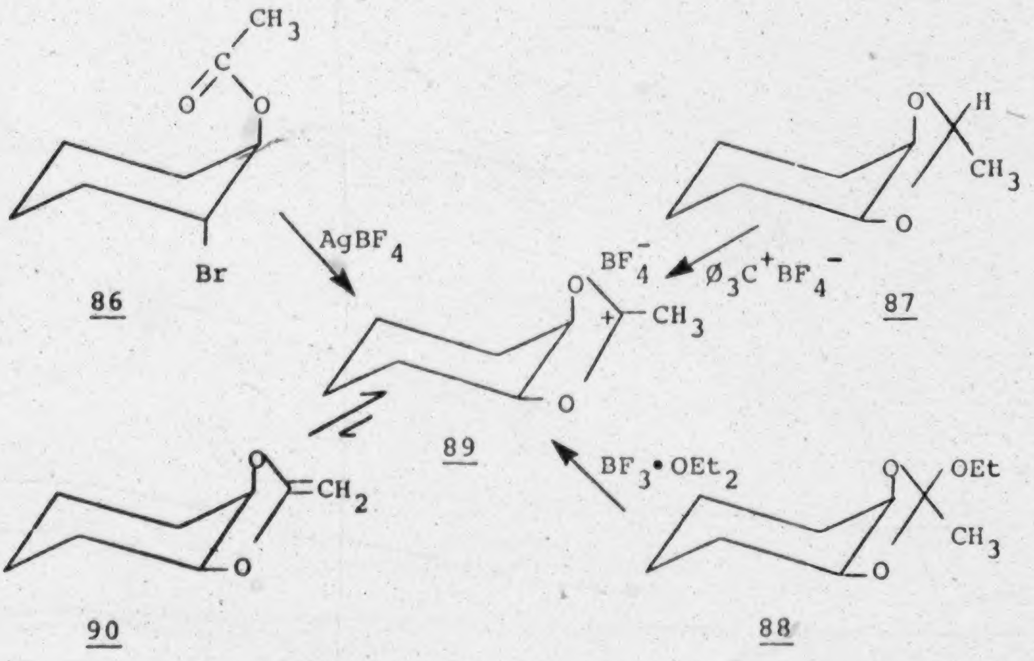
isolated the first stable trialkyloxonium salts at this same time,[116] and later prepared 2-methyl-1,3-dioxolan-2-ylium tetrafluoroborate (83) by reaction of 2-bromoethyl acetate (82) with silver tetrafluoroborate.[117] Meerwein also obtained 83 from treatment of the orthoester 84

(2-ethoxy-1,3-dioxolane) with borontrifluoride etherate.[118] Reaction of 83 with lithium chloride, hydrogen bromide, or sodium iodide was found to give the corresponding halohydrin esters (85).



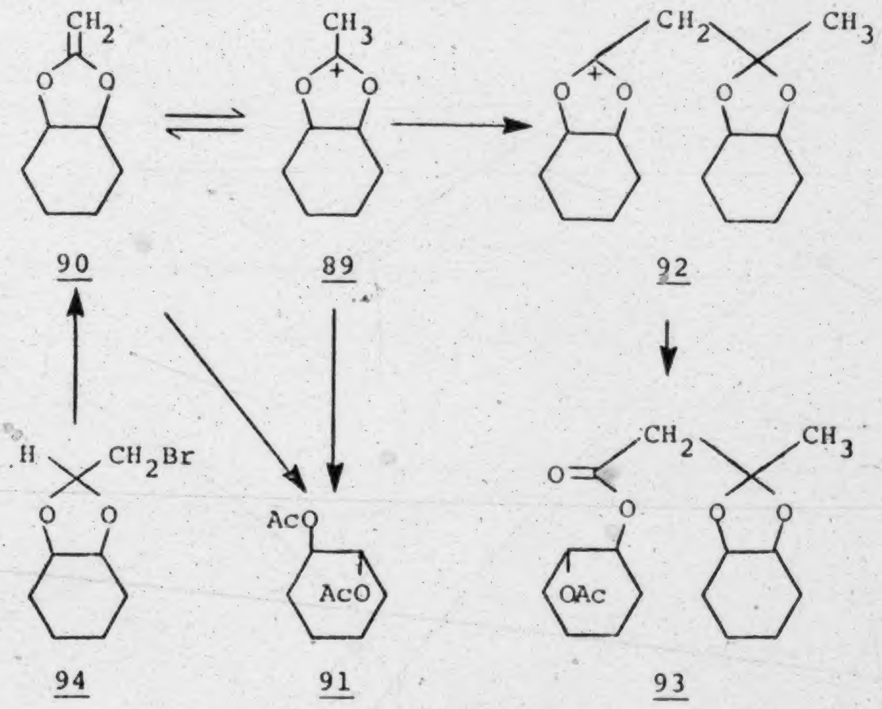
Scheme XVII

Another pertinent example regarding the preparation and properties of acyloxonium ions can be found in Winstein's studies of the 2-methyl-(cis-4,5-tetramethylene)-1,3-dioxolan-2-ylium ion (89). This ion was prepared by treating trans-2-acetoxycyclohexyl bromide (86) with silver tetrafluoroborate, by reaction of the acetal (87) with trityl tetrafluoroborate, and from the orthoester (88) by treatment with borontrifluoride etherate.[119] The nmr spectrum of 89 in deuterioacetic acid showed a rapid exchange of the 2-methyl protons, indicating an equilibrium with the ketene acetal (90). The equilibrium, even in an acid of such modest strength as acetic, lay far to the side of the ion.



Scheme XVIII

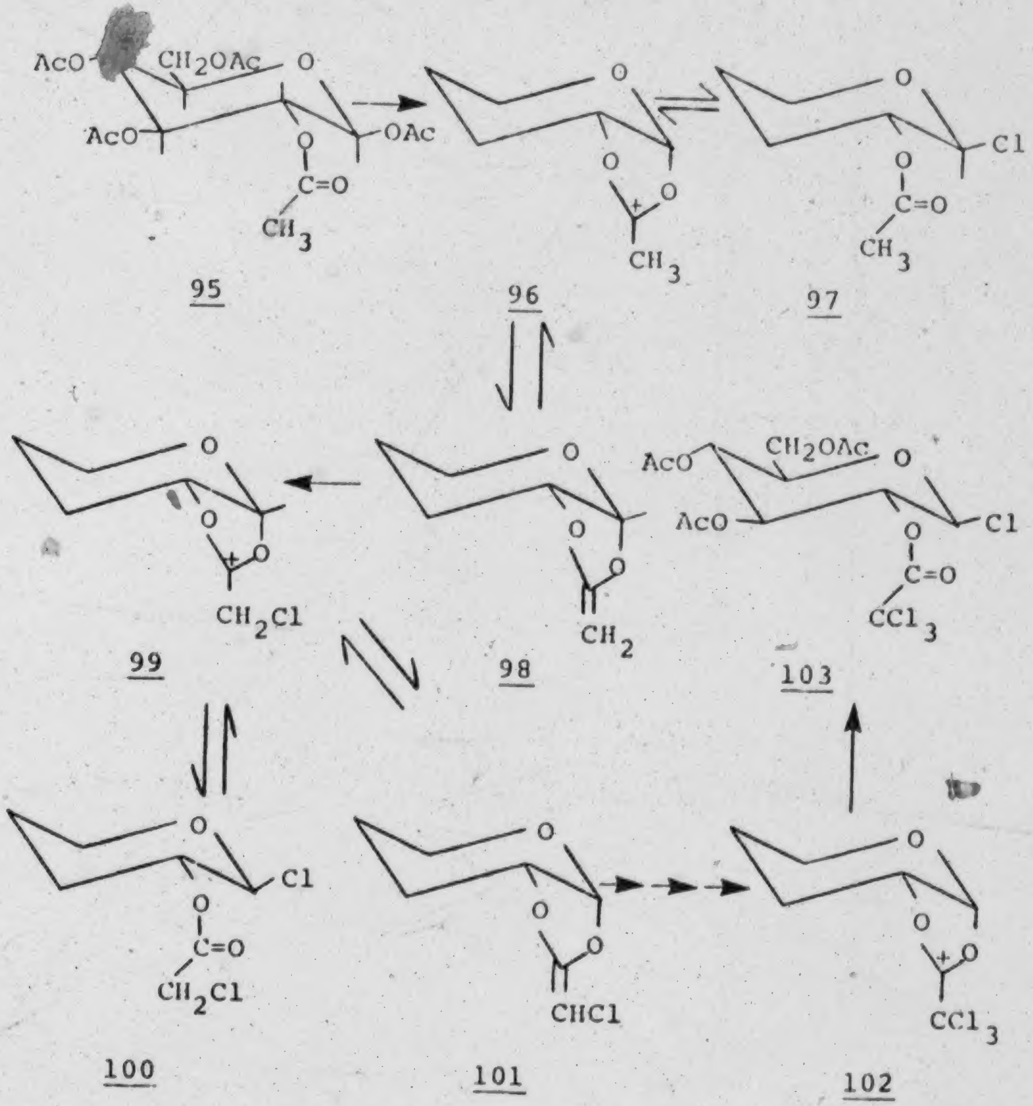
The equilibrium formation of 90 is also evident in the reactions of 89. For example, treatment of 89 with potassium acetate in acetic acid gives about 50% of the product of simple displacement, of which 94% is the *trans* isomer 91, and 50% of a dimeric product, 93. The latter product is thought to arise from reaction of 89 with the ketene acetal 90 to give the substituted acetoxonium ion 92, which is opened with acetate ion to give the observed product (93). Winstein and coworkers had earlier prepared this ketene acetal by treatment of the bromoacetal 94 with potassium t-butoxide.[120] They could obtain good yields of 91 from 90 by slow addition of the ketene acetal to anhydrous acetic acid. Rapid addition gave polymerization, analogous to the dimerization observed in the solvolysis of 89. The presence of a very low concentration of the ketene acetal effectively precludes polymerization in the latter case.



Scheme XIX

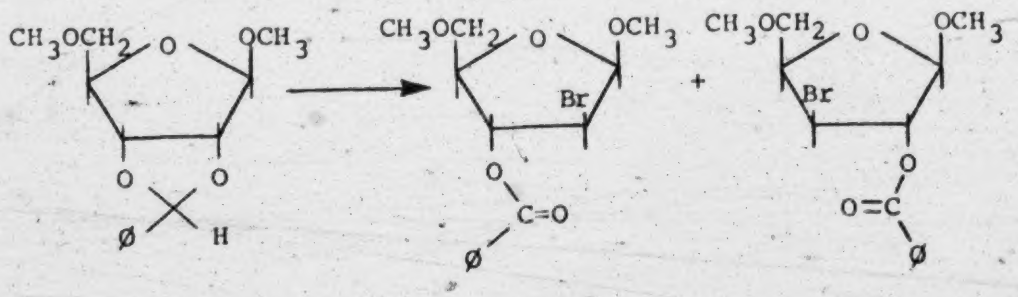
Further evidence for the existence of ketene acetals in equilibrium with acyloxonium ions has recently been provided by Schroeder.[121] In an nmr study of the acid catalyzed alcoholysis of trimethylorthoacetate, triethylorthoacetate, and 2-ethoxy-2-methyl-1,3-dioxolane (84), a rapid alkoxy exchange was observed, in the latter case involving only the ethoxy group. The alkoxy exchange was accompanied by a slower exchange of the orthoacetyl methyl protons, which was explained as proceeding via the ketene acetal. Since there was no evidence of the accumulation of ketene acetal, the elimination step is seen to be rate controlling for the deuterium exchange. Alkoxy exchange, which operates largely through the acetoxonium ion itself, was very rapid relative to the deuterium exchange.

A very early indication of the intervention of ketene acetals was discerned by Freundenberg and Scholz.[122] They suggested that the formation of 3,4,6-tri-O-acetyl-2-O-trichloroacetyl-β-D-glucopyranosyl chloride (103) from treatment of penta-O-acetyl-β-D-glucopyranose (95) with phosphorous pentachloride[123] involved conversion of the acetoxonium ion to a ketene acetal (98) which was then chlorinated to give 99 . Successive elimination and chlorination gave the trichloroacetoxonium ion (102) which was attacked by chloride ion to give 103. Although each acyloxonium ion can be opened by chloride attack to give the corresponding glycosyl chloride, this reaction is reversible , and the final product is therefore the 2-O-trichloroacetyl compound (103).



Scheme XX

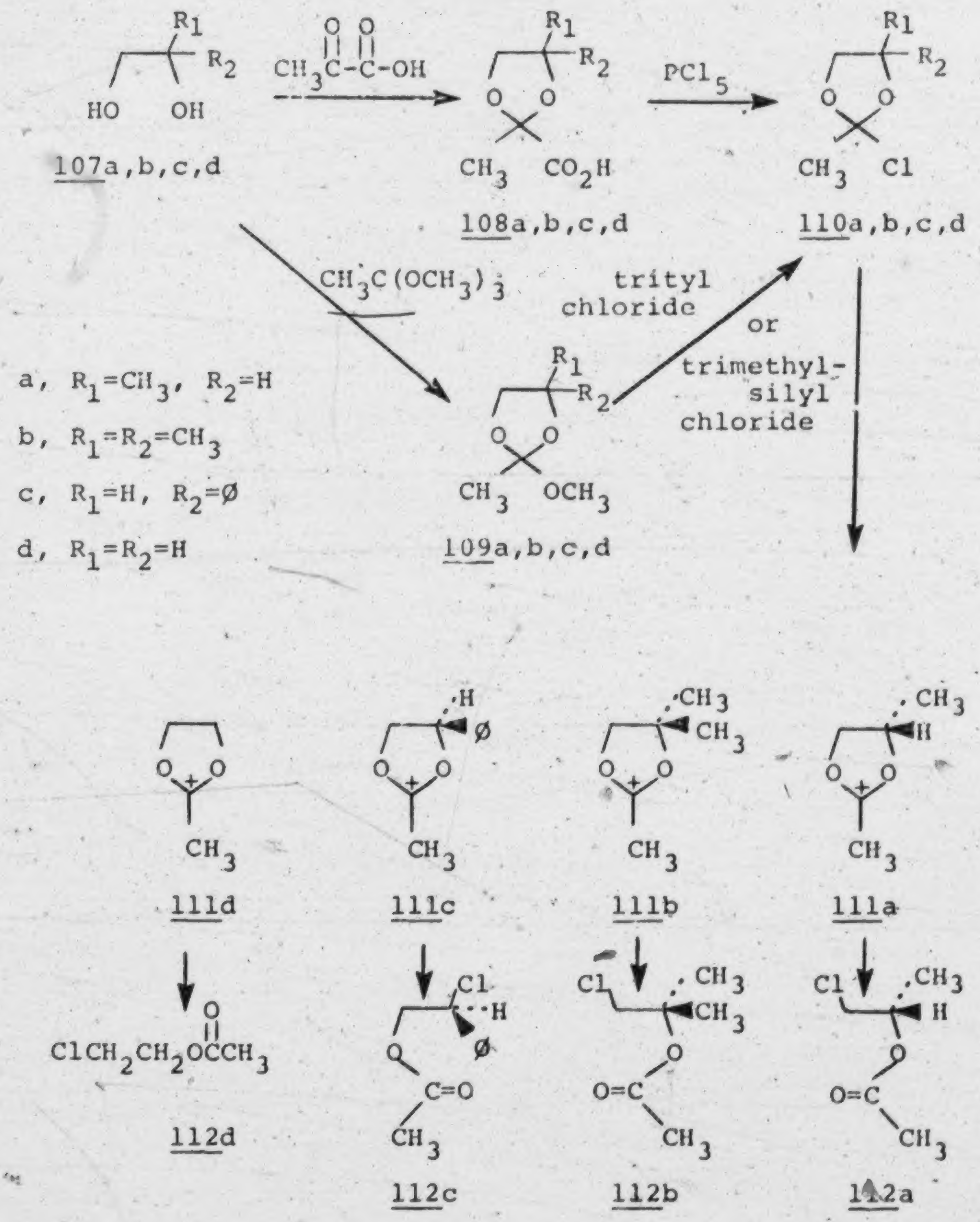
The literature on acyloxonium ions is now quite extensive and has been the subject of several recent reviews.[124-129] However, there are relatively few examples of the generation of acyloxonium ions from a *cis* 1,2-diol system such as is present in the common ribonucleosides. The work of Hanessian *et al*. with 2',3'-O-benzylideneuridine (65) has already been mentioned in this regard. Before applying the reaction to this nucleoside, extensive studies were pursued in carbohydrate syntheses. One of these studies involved the reaction of NBS with methyl 2,3-O-benzylidene-5-O-methyl-β-D-ribofuranoside (104) to give methyl 3-O-benzoyl-2-bromo-2-deoxy-5-O-methyl-β-D-arabinofuranoside (105) and methyl 2-O-benzoyl-3-bromo-3-deoxy-5-O-methyl-β-D-xylofuranoside (106) in approximately equal amounts. Thus, for secondary sites of similar electronic and steric environments, both possible products are formed, as expected.



104 105 106

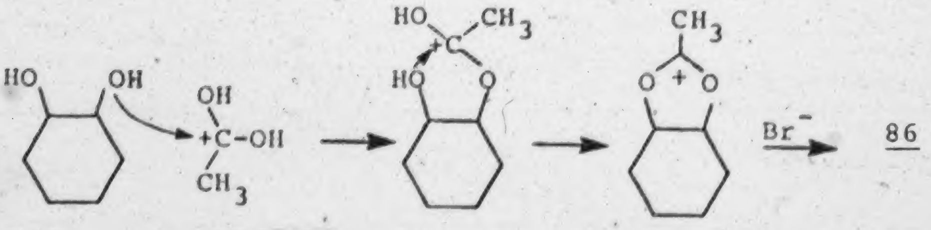
Scheme XXI

Newman and coworkers have recently published several articles on the conversion of diols to trans chlorohydrin esters.[130-132] This has been accomplished by conversion of the diol to an α-ketal acid (108) followed by reaction with phosphorous pentachloride, or by conversion of the diol to an orthoester (109) followed by reaction with either trityl chloride or trimethylsilyl chloride. In each case the product for a particular diol is the same, since each reaction proceeds via an acetoxonium ion (111) in the final step. The existence of 2-chloro-2-methyl-1,3-dioxolane species such as 110d was indicated by nmr spectroscopy. The reaction of 108d was carried out at -60 to -70° and the nmr spectrum measured at -58°. In this way methyl and methylene resonances at δ 1.66 and 4.14, respectively, were observed. On warming the sample to 0° the spectrum rapidly rearranged to that of α-chloroethyl acetate (112d), without exhibiting the resonances characteristic of the acetoxonium ion (111d). The spectrum of this acetoxonium ion, as its tetrafluoroborate salt (83) had been measured previously, and shows peaks at δ 2.67 and 5.21 for the methyl and methylene resonances.[119] The regiospecificity of nucleophilic opening of the acetoxonium ion is apparent from the nearly exclusive formation (≥96%) of 112a, 112b, and 112c. Thus for 111a and 111b attack occurs at the less hindered primary center. However, in the presence of a group


107a,b,c,d
$CH_3C(O)-C(O)-OH$
108a,b,c,d
PCl_5
110a,b,c,d
$CH_3C(OCH_3)_3$
109a,b,c,d
trityl chloride
or
trimethylsilyl chloride
a, $R_1=CH_3$, $R_2=H$
b, $R_1=R_2=CH_3$
c, $R_1=H$, $R_2=\emptyset$
d, $R_1=R_2=H$
111d
111c
111b
111a
$ClCH_2CH_2OCCH_3$
112d
112c
112b
112a

Scheme XXII

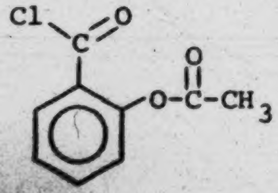
which can stabilize the positive charge of bond breaking, or partial bond breaking, this steric control is reversed. Attack occurs in 111c at the electronically stabilized benzylic secondary position. Analogous regiospecific results for 107a and 107c have been obtained by Golding using hydrogen bromide in acetic acid on the diol itself.[133] This reaction was shown to proceed with cis cyclohexane diol (113) via monoacetylation of the diol to give 115 followed by formation of the acetoxonium ion 116, which is then opened by bromide ion. The presence of the 2-methyl-(cis-4,5-tetramethylene)-1,3-dioxolan-2-ylium ion (116) was shown by the appearance in the nmr of signals at δ 2.90 and 5.92 for the methyl and methine protons, respectively. These values are consistent with those obtained by Winstein for the tetrafluoroborate salt (89) which were δ 2.72 and 5.70. As the reaction progresses these signals disappear, as expected.



113 114 115 116

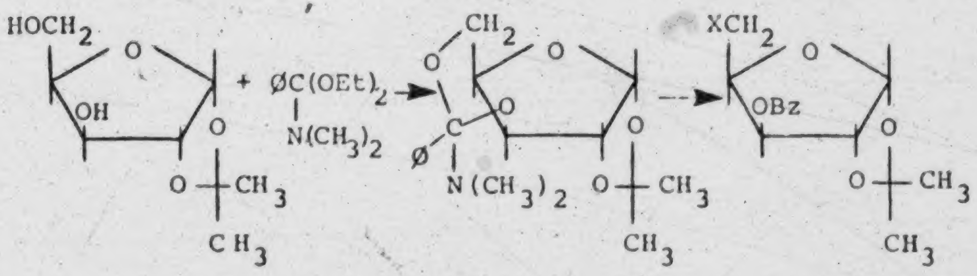
Scheme XXIII

In addition to this regiospecificity, both Newman and Golding, using simple optically active diols (107a and c), have determined that a net inversion of configuration about the carbon subjected to nucleophilic attack has occurred. This SN_2 character is also apparent in those reactions (NBS or α-acetoxyisobutyryl halide procedures) which have been applied to carbohydrates or to purine nucleosides, where conversion of the product to an epoxide has been used to demonstrate a trans configuration. Recently a report on the use of acetylsalicyloyl chloride (117) with diols to give the analogous halohydrin acetates has appeared.[134] This work supports the regiospecificity demonstrated above for 107a. However, the authors favor an SN_i or tight ion pair mechanism for the collapse of an intermediate 2-chloro-2-methyl-1,3-dioxolane (110). Newman has suggested that such a tight ion pair mechanism requires largely retention of configuration, whereas inversion has been found.[130] In fact, Akhrem et al. have not presented any evidence that is not compatible with the accepted SN_2 mechanism.



117

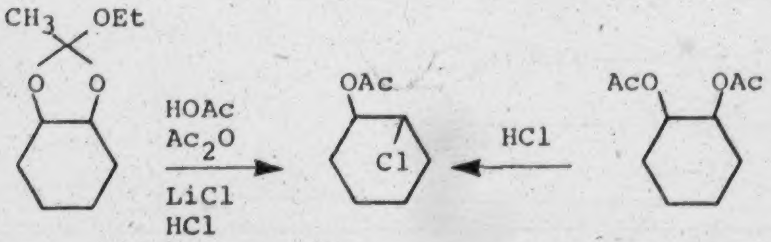
The α-(dimethylamino)benzylidene group has also been used for entry into acyloxonium ion reactions. It was first reported by Hanessian as a blocking group[135] and has recently been used to prepare halohydrin ester derivatives.[136] In this case 3,5-O-α-(dimethylamino)-benzylidene-1,2-O-isopropylidene-α-D-xylofuranose (120), prepared by treatment of the 1,2-O-isopropylidene compound (118) with N,N-dimethylbenzamide diethylacetal (119), was reacted with ethyl iodide, cyanogen bromide, and n-propylbromide. The exclusive product (121) was that of attack at the primary 5-position.



118 119 120 121

Scheme XXIV

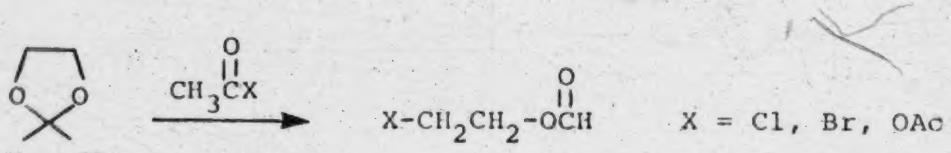
In work mentioned above Winstein has converted the cyclohexane acetoxonium ion 89 to the expected trans chloro and bromo derivatives and has obtained the chloro derivative (122) directly from the orthoester (88) by treatment with a mixture of acetic acid, acetic anhydride, lithium chloride and hydrogen chloride.[137] Treatment of cis-1,2-diacetoxycyclohexane (123), but not the trans isomer, has also been shown by Winstein to give largely 122 and deacetylated 122.[138] The mechanism was formulated as an initial monodeacetylation followed by cyclization to the acetoxonium ion and attack by chloride ion. It was also shown that cis-1,2-cyclohexane diol (113) gave the same product when treated with hydrogen chloride in acetic acid, analogous to Golding's later use of hydrogen bromide in acetic acid (Scheme XXIII).



88 122 123

Scheme XXV

An approach using reaction of an orthoformate with an acetyl halide or acetic anhydride was reported in 1958.[139] The reaction of the ethylorthoformate of ethylene glycol (2-ethoxy-1,3-dioxolane) (124) with acetyl chloride, acetyl bromide, or acetic anhydride was shown to give the corresponding 2-halo or 2-acetyl-ethyl formate (125).

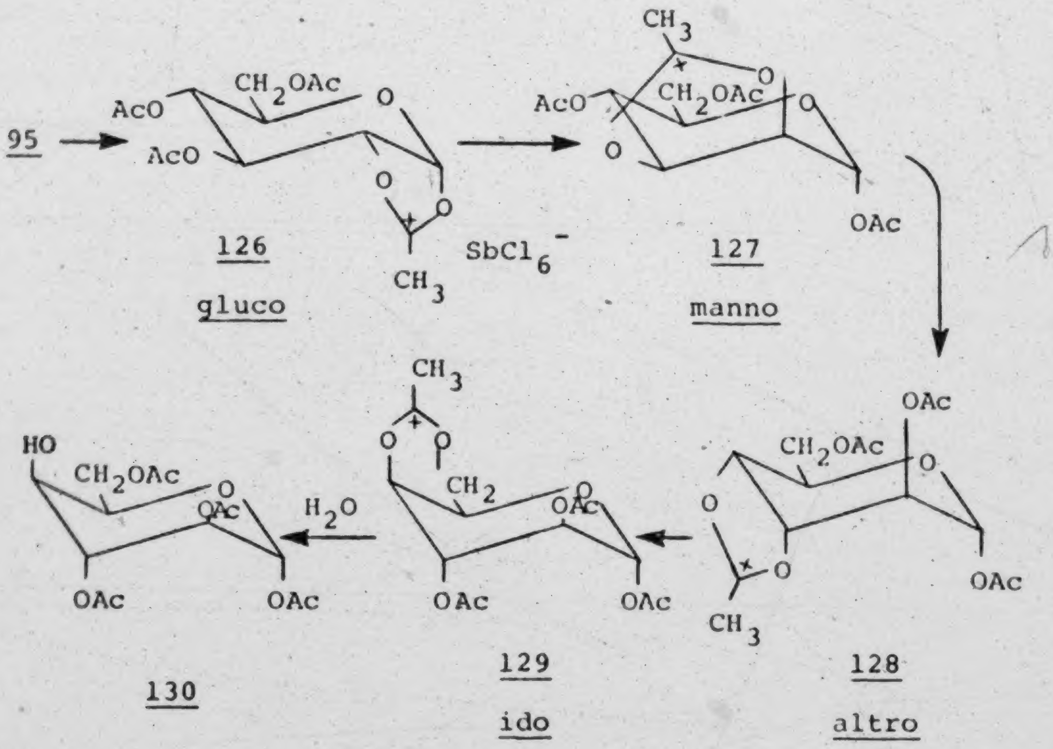


124

125

Scheme XXVI

Paulsen has studied the equilibration of acyloxonium ions[140] and has used it to effect rearrangement of a *gluco* (126) to an *ido* (129) derivative.[141] The intermediacy of *manno* (127) and *altro* (128) derivatives is required in this scheme, which represents a quite different synthetic application of acyloxonium ions.



Scheme XXVII

DISCUSSION

A. REACTIONS OF 2',3'-*O*-METHOXYETHYLIDENEADENOSINE WITH PIVALYL HALIDE.

The syntheses to be described in this section developed from the observation by Robins of the ease of conversion of 3',4'-*O*-ethoxymethylidene psicofuranine into the 1',3',4'-*O*-orthoformate derivative with boron trifluoride etherate, mentioned previously in the synthesis of the antibiotic decoyinine (Scheme XI). Adenosine was chosen as the primary substrate for this work because of its central role in nucleic acid and energy metabolic pathways including coenzymes, the multiplicity of nucleoside antibiotics "derived" from it, and because of its ready availability as a synthetic starting material. Accordingly, 2',3'-*O*-methoxyethylideneadenosine (*131*), routinely prepared in near quantitative yield by a modification of the procedure reported by Reese,[142,143] was treated with boron trifluoride etherate or antimony pentachloride in the presence of iodide ion. However, the main product in these reactions was invariably 2'(3')-*O*-acetyladenosine.[143] Since our primary interest lay in developing a high yield conversion to halogenated derivatives, other methods were sought. Recently Moffatt reported that boron trifluoride etherate could be used to obtain moderate yields (33-35%)

of 3'-iodo- and 3'-bromo-3'-deoxy-2'-O-acetyladenosine, along with an unspecified amount of 2'(3')-O-acetyladenosine.[111] This appears to confirm our earlier conclusion that boron trifluoride etherate did not afford a practical route for obtaining high yields of halogenated nucleosides. Our studies turned next to pyridine hydrohalide, which was found to be only weakly effective, and then moved to the use of acyl halides in pyridine solution.[143] Acetyl halides were found to be unsatisfactory,[143] possibly by virtue of their decomposition to ketene under the conditions (refluxing pyridine) which were used.[144] It was subsequently found that this problem could be overcome, and the desired transformation obtained, through the use of pivalic acid chloride in refluxing pyridine.[110-112] The expected 6-N-pivalamido-9-(3-chloro-3-deoxy-2-O-acetyl-5-O-pivalyl-β-D-xylofuranosyl)purine (134) was isolated in 70% yield, along with some of the 2'-chloro-*arabino* isomer. Although no attempt was made to separate them in the present study, the deblocked 2'-chloro isomer has been isolated and characterized in this laboratory.[145] When the reaction was effected at room temperature the product of simple pivalyation (132) was isolated. This compound gave the same products as did 131 when reacted at reflux. Thus it is likely that formation of the acetoxonium ion (133) is catalyzed by pivalyl chloride (or its pyridinium complex) and not by the pyridine hydrochloride produced in conversion of 131 to 132.

In addition to 134 another product was formed in 11% yield. Like 134, the ultraviolet maximum was at 272nm, indicating that the material was 6-N-acylated. Treatment with sodium methoxide rapidly converted it to 2',3'-anhydroadenosine, indicating that it was also a 2',3'-trans-halohydrin derivative. In this case the nmr spectrum (Figure 1) lacked the acetyl resonance at δ 2.18 observed in the spectrum of 134 (Figure 2) and had two additional t-butyl resonances at δ 1.16 and 1.25. A further sharp singlet occurred in the vinyl region at δ 5.76 corresponding to one proton. The spectra (Figures 1 and 2) were otherwise analogous. The mass spectrum of this minor component showed a parent ion at m/e 663. This was 168 units higher than that of 134, at m/e 495. A difference of 168 is compatible with the "substitution" of two pivalyl groups (mass of 85), for two of the protons of 134. Absence of the acetyl methyl signal in the nmr spectrum suggested substitution at that position. Attempts to convert the acetyl compound (134) to this m/e 663 component by treatment of 134 with pivalyl chloride in refluxing pyridine, as in the original reaction, were unsuccessful. The m/e 663 component must therefore result from some intermediate species.

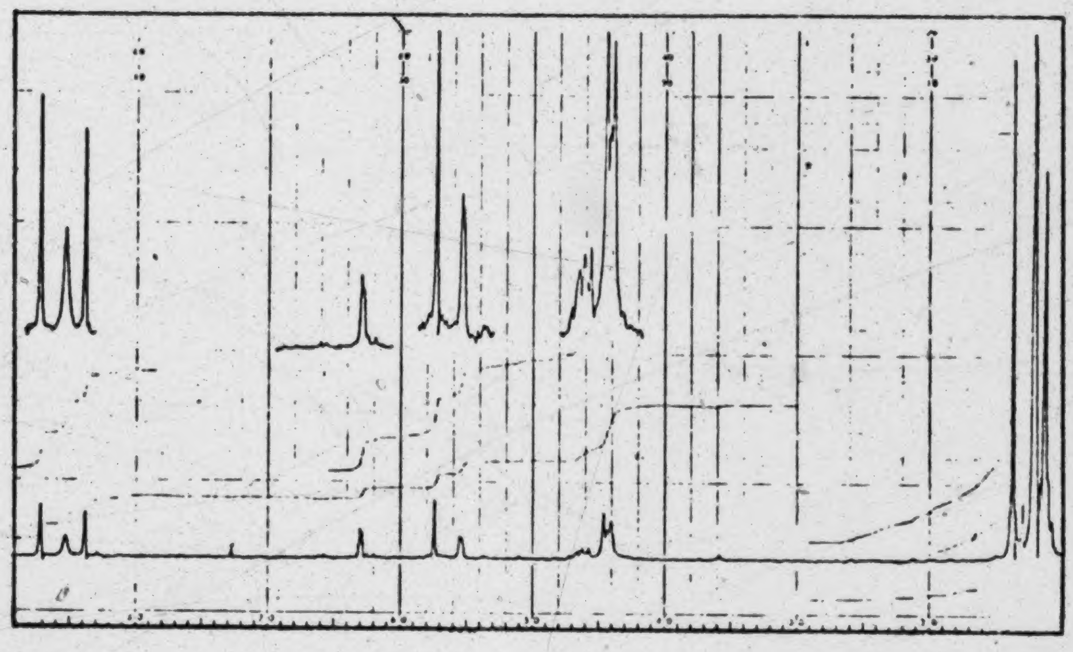


Fig. 1. 6-N-Pivalamido-9-(3-chloro-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)-purine (141) ($CDCl_3$).

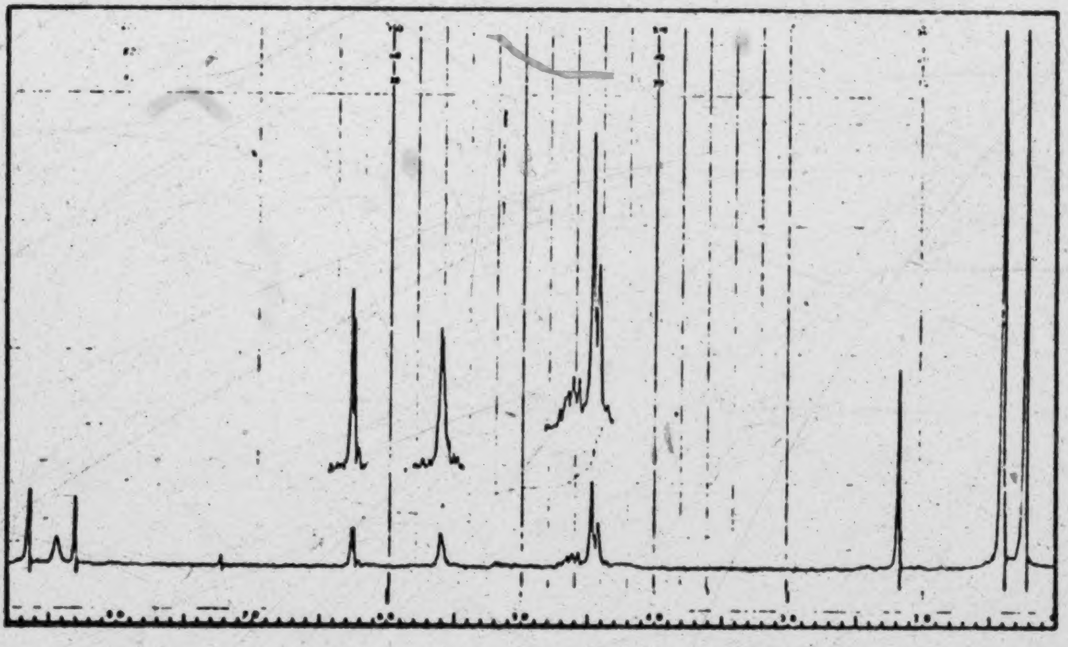
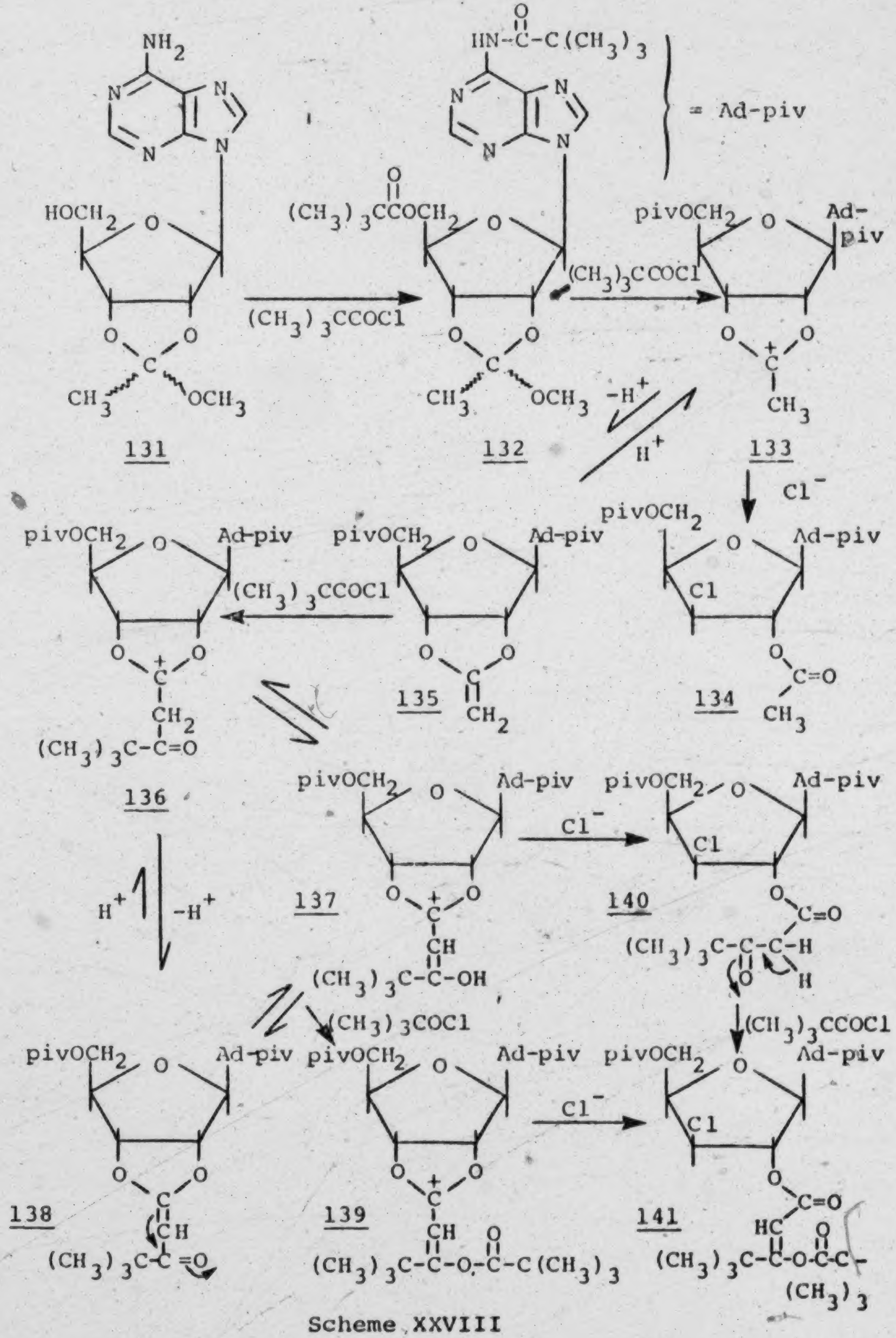
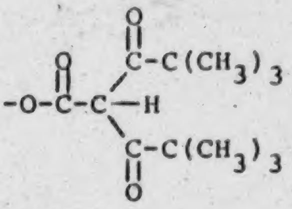


Fig. 2. 6-N-Pivalamido-9-(3-chloro-3-deoxy-2-O-acetyl-5-O-pivalyl-β-D-xylofuranosyl)purine (134) ($CDCl_3$).

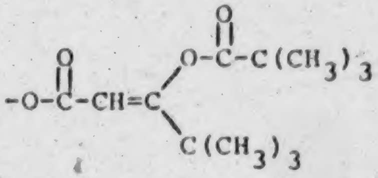


Scheme XXVIII

It was mentioned above that acetoxonium ions exist in equilibrium with the corresponding ketene acetals. Thus in the present case some of the ketene acetal 135 could be present. If this ketene acetal were acylated by pivalyl chloride, the substituted acetoxonium ion 136 would be formed. This ion, or its tautomer 137, could be opened by a chloride ion to give 140. Alternatively, 136, 137 or the corresponding pivalylated ketene acetal (138) could be further acylated to produce acetoxonium ion 139. Opening of 139 by chloride attack would give the 4,4-dimethyl-3-pivaloxypent-2-enoyl derivative (141). The structure of this enolester compound is consistent with the nmr and mass spectral data described previously. The latter acylation could also potentially be a C-acylation which would lead to the dipivalylacetoacetic ester fragment 142. Although the remaining "acetyl" proton of 142 should be readily exchangeable, the vinyl proton of 143, the O-acylated fragment, should not be. In fact, no exchange of the signal at δ 5.76 was observed, either on long standing or on warming in 95% per deuterated ethanol/deuterium oxide.



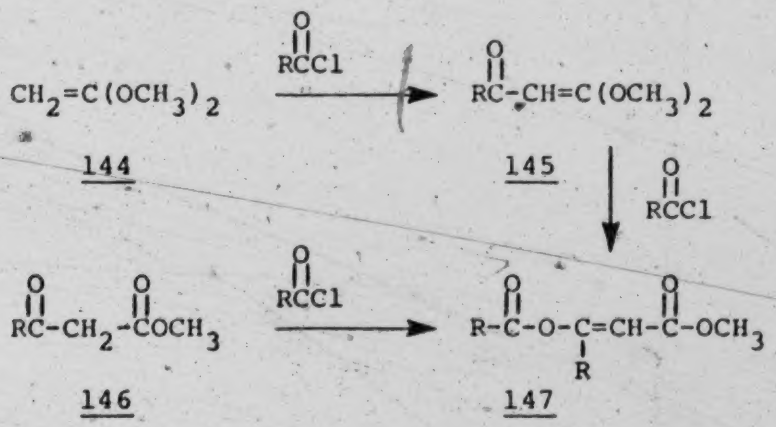
142



143

Ketene acetals, in addition to being intermediates in equilibrium with an appropriate acyloxonium ion, have been prepared and studied themselves, principally by McElvain and coworkers. The syntheses have been accomplished by three main routes: dehydrohalogenation of α-bromoacetals;[146] the reaction of sodium with α-bromoorthoesters;[147] and the dealcoholation of orthoesters. This dealcoholation can be achieved by either simple pyrolysis,[148] or reaction with an aluminum alkoxide usually aluminum *t*-butoxide.[149] Both McElvain[150] and Borrmann[151] have reviewed ketene acetals in detail.

McElvain found that reaction of ketene dimethyl acetal (144) with acyl chlorides gave two main products: the acylketene acetal (145) and the *O*-acyl derivative of a β-ketoester (or enolester 147).[152] The relative yields were dependent both on the ratio of the reactants and the nature of the acyl chloride. A 4:1 ratio of ketene acetal to valeryl chloride, for example, gave 24% of acylketene acetal (145) and 63% of enolester (147), while a 20:1 excess gave yields of 56% and 28% respectively. However, reaction at the 4:1 ratio with pivalyl chloride was sufficient to give a 75% yield of acylketene acetal. It was apparent from these results that the acylketene acetal (145) produced from reaction with the straight chain acyl chlorides was more readily acylated than was the starting ketene acetal.[152] A large excess of ketene acetal is thus required to obtain good yields of 145. This situation is largely reversed with the α,α,α-trisubstituted acyl chloride, pivalyl chloride, presumably by steric inhibition of acylation at the carbonyl of 145. It was demonstrated both by McElvain[153] and earlier by Claisen,[154] that acylacetic esters (146) are readily O-acylated to the corresponding enolesters (147) in the presence of a proton acceptor. In McElvain's work the proton acceptor was excess ketene acetal and in Claisen's it was pyridine. This facile O-acylation may be the reason that acylacetic esters (146) were not isolated in more than trace amounts in the acylations of ketene dimethylacetal (144).

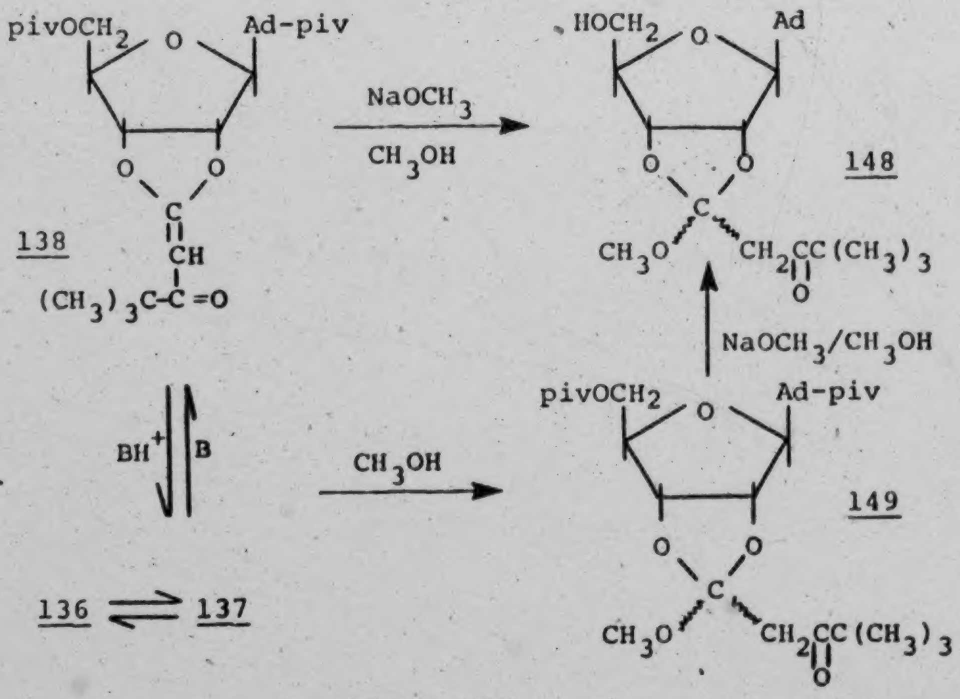


Scheme XXIX

In light of McElvain's studies, it should be possible to isolate the pivalylketene acetal (138) under conditions of incomplete reaction, if the mechanism shown in Scheme XXVIII is correct. This was accomplished by conducting the reaction at 50° for 66 hours rather than two hours at reflux. The pivalylketene acetal (138) is a very polar compound on tlc (silica, 3% methanol in ether) and 22% yield of 138 was obtained by direct crystallization of the crude reaction mixture from ether. Chromatography of the mother liquors on a silica column gave 10% of the enolester derivative (141), 4% of the blocked orthoester (132), 21% of the acetyl derivative (134) and an additional 14% of 138. Higher reaction temperatures resulted in increased formation of 134 while at lower temperatures the reaction did not proceed beyond the blocked orthoester (132) at reasonable rates. The pivalylacetic ester compound (140) corresponding to nucleophilic opening of 136 or 137 has not been detected. Presumably if this compound were formed it would be readily O-pivalylated to the enolester (141), since the ratio of pivalyl chloride to orthoester used in these reactions was 10:1. The isolation of appreciable quantities of 138 suggests that it is favored over the pivalylated acyloxonium ion (136) or its allylic acyloxonium tautomer (137), even in the presence of pyridine hydrochloride. This is contrary to the situation with unsubstituted acyloxonium ions, which have not been directly observed in the presence of acids.[63,121] Presumably this reversal is due to the stabilization afforded by the conjugated system of the acylated ketene acetal.

The products formed in the reaction of 2',3'-O-methoxyethylideneadenosine (131) with pivalyl chloride are thus dependent on the rate of acylation of the ketene acetal (135) relative to the rate of nucleophilic attack on the initial acyloxonium ion (133). Reduction of the rate of chloride attack, by lowering the reaction temperature, allows the weakly acylating pivalyl chloride to compete more successfully. Since this acylation is not reversible, the net effect is an increase in the ratio of enolester to acetyl products from 1:7, for the reaction at reflux, to 1:2 for the reaction at 50°.

Treatment of the crude mixture from reaction of 131 with pivalyl chloride (at reflux) with sodium methoxide in methanol gave a low yield of an ether extractable material. This was found to be a substituted orthoester, 2',3'-O-(methoxy pivalylethylidene)adenosine (148). Although 148 was only formed in low yield by this procedure, it was available in reasonable quantity as a by-product from the large scale preparations of 2',3'-anhydroadenosine carried out in this laboratory.[155] The formation of 148 has been shown to proceed from 138 by either of two routes. After these pivalyl chloride reactions had cooled sufficiently, methanol was added to destroy the excess pivalyl chloride. Under these conditions 138 was converted to the blocked pivalylethylidene orthoester (149) which, upon methoxide treatment, gave 148. However, this reaction of 138 with methanol is slow at room temperature. The same procedure was followed in the preparation of 138 described above, where the reaction was carried out at 50°, and only traces of 149 were detected after stirring with methanol for one-half hour. Complete conversion of 138 to 149 requires about 24 hours at room temperature, but can be accelerated by warming. This may proceed either by conversion of the pivalylketene acetal (138) to one of the substituted acyloxonium ions, 136 or 137,

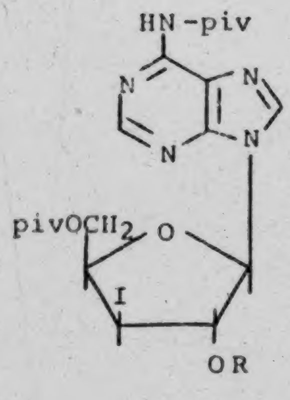


Scheme XXX

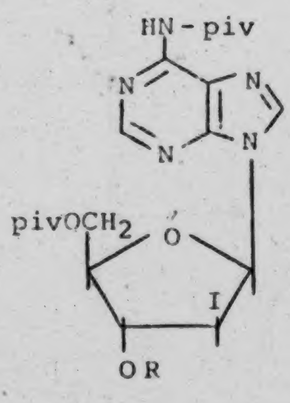
followed by reaction with methanol, or by a Michael addition of methanol on 138 itself. In fact, treatment of 138 with sodium methoxide in methanol gave 148 after a few hours at room temperature. The use of ethanol rather than methanol, to destroy the pivalyl chloride, followed by treatment with sodium ethoxide, gave the corresponding ethoxy pivalylethylidene orthoester as required by the above rationale. When treated with pivalyl chloride in refluxing pyridine only the enolester derivative 141 was formed from 148 or 149. However, the reaction was very slow and even after five hours at reflux considerable 149 remained. The pivalylketene acetal (138) was also present under these conditions. It is apparent that formation of the pivalyloxonium ion (136) from the pivalylethylidene orthoester (149) is more difficult than is formation of acetoxonium ion (133) from the unsubstituted orthoester (132). This is presumably due to the inductive withdrawal of the carbonyl in 149, decreasing protonation or acylation of the orthoester methoxyl or oxygen and/or increasing the strength of the orthocarbonyl carbon-oxygen bonds.

The chloro-deoxy compounds (134 and 141) have proved very useful for preparing 2',3'-anhydroadenosine,[155] and for reduction to the deoxy derivatives by a free radical route.[143] However, a facile general route to the synthesis of deoxy and unsaturated nucleosides from the halo derivatives was desired. Accordingly, the iodo-deoxy derivatives were prepared because of their greater ease of hydrogenolysis and elimination. This was accomplished by the addition of pivalyl chloride to a refluxing solution of 2',3'-*O*-methoxyethylidene-adenosine (131) and excess sodium iodide. In this case the reaction required only four minutes at reflux, rather than two hours, and none of the iodo-acetyl compound corresponding to 134 was isolated. Instead, the observed products are 6-*N*-pivalamido-9-(3-iodo-3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-*D*-xylofuranosyl)purine (150), the 2'-iodo-arabino isomer (151), the 3',4'-unsaturated compound (152), corresponding to elimination of hydrogen iodide from (150), and a trace of 6-*N*-pivalamido-9-(5-pivaloxymethyl-2-furanyl)purine (153). The acylating ability of acyl halides is known to increase in the order F<Cl<Br<I,[156] and a stronger acylating agent would be expected to react more efficiently with the ketene acetal (135) thus driving the reaction to the enolester derivatives. This result is therefore consistent with the mechanism shown in Scheme XXVIII.

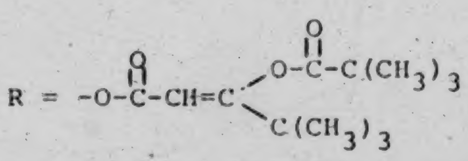
The experiments previously described for the reaction of pivalyl chloride with certain products of the initial reaction have also been carried out with pivalyl chloride/sodium iodide. Treatment of the chloro-acetyl



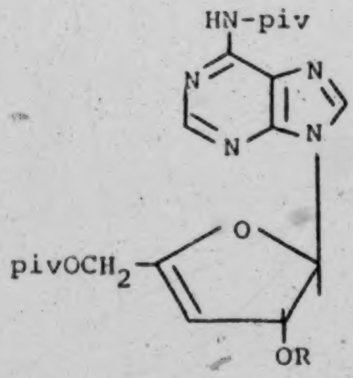
150



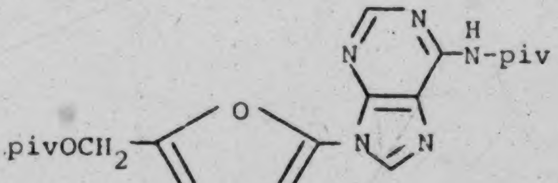
151



$R = -O-\overset{O}{\overset{\|}{C}}-CH{=}C\begin{cases} O-\overset{O}{\overset{\|}{C}}-C(CH_3)_3 \\ C(CH_3)_3 \end{cases}$



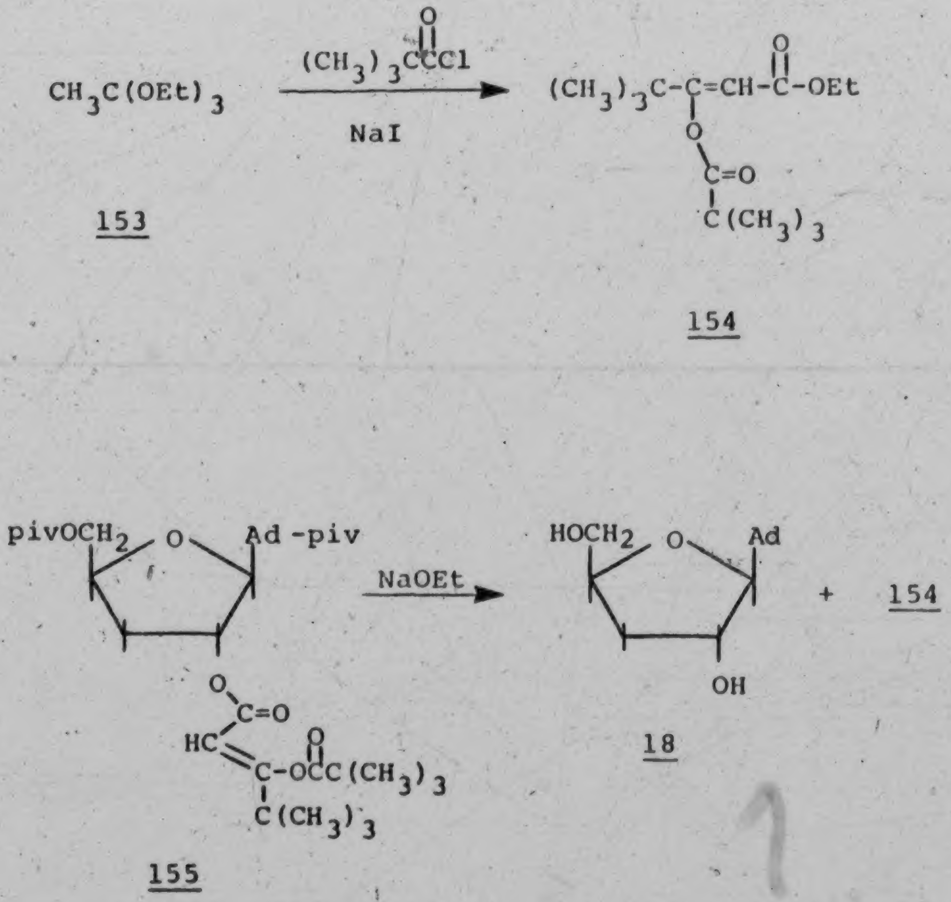
152



153

compound (134), with pivalyl chloride/sodium iodide in refluxing pyridine gave no reaction, while similar treatment of the blocked orthoester (132) gave the same product mixture as did 131. Although reaction of the pivalylethylidene orthoester (148) was faster here than in the absence of sodium iodide, it was still very slow and no pivalylketene acetal (138) was observed. Finally, reactions run at lower temperatures in an attempt to prepare 138 were unsuccessful. Instead, only mixtures of the orthoester 132 and enolester derivatives 150 and 151, as well as some of the 3',4'-unsaturated compound 152, were obtained. However, intermediacy of the pivalylketene acetal was indicated since treatment of 138 in the same manner as 131 gave the same product mixture in analogous yields. Failure to isolate significant amounts of 138 in the presence of sodium iodide under conditions of incomplete reaction suggests that the subsequent acylation of 138 to 139 has been enhanced to a greater extent than has the rate of formation of the initial acetoxonium ion (133). This may be rationalized on the basis that conversion of 132 to 133 involves a large bond-breaking factor. The importance of this bond-breaking is manifested in the low rate of reaction of the pivalylethylidene orthoester 149, although steric effects may also be critical. It may be argued that pivalylation of 138 to 139 is the major or exclusive pathway to enolester derivatives since 138, in the absence of acid, reacts at the same or a greater rate than does 131. However, the possibility that sufficient acid was present for reaction to actually proceed via 136 or 137 cannot be excluded, since no reactions were carried out in the presence of acid scavengers.

A final observation on this reaction and the identity of the product enolester was obtained from synthesis of the enolester moiety itself by an analogous route. Upon addition of triethyl orthoacetate (153) to a solution of pivalyl chloride and sodium iodide in pyridine, an exothermic reaction occurred from which an 11% yield of ethyl-4,4-dimethyl-3-pivaloxypent-2-enoate (154) was distilled and crystallized. The mechanism is presumably



Scheme XXXI

analogous to that described in Scheme XXVIII. The same compound, identical by mixed melting point, nmr, and infrared spectra, could be obtained in 50% yield by the action of sodium ethoxide on the 3'-deoxy-2'-O-enolester compound (155) derived from hydrogenolysis of the 3'-iodo-3'-deoxy-2'-O-enolester product (150). The vigorous reaction of the simple orthoester is indicative of the strongly inhibiting effect of the bulky and electronegative nucleoside on this reaction.

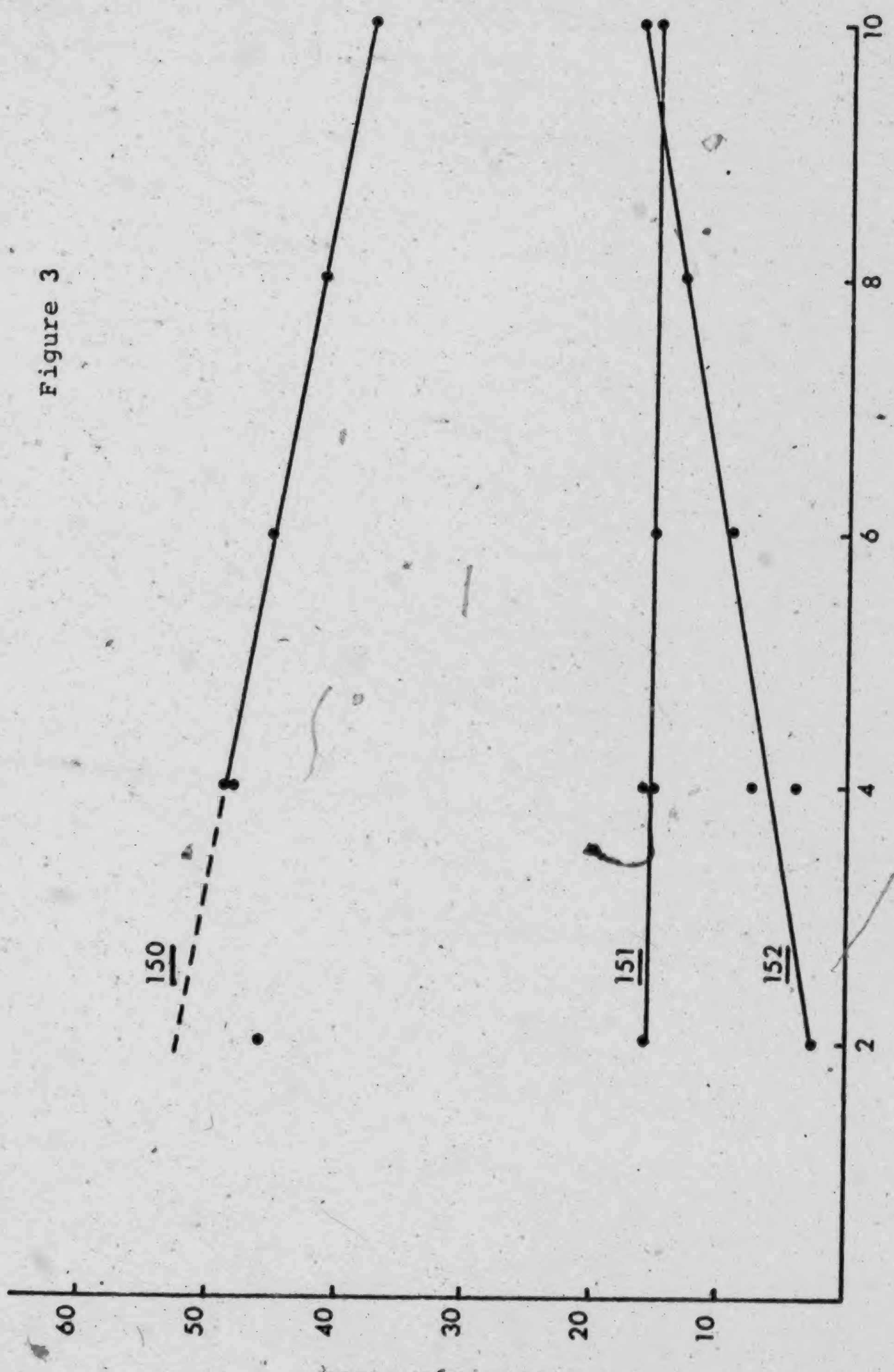
The ethyl enolester (154) has an ultraviolet maximum at 216 nm, analogous to the maxima reported by McElvain for other aliphatic enolesters,[152] strong absorption in the infrared at 1645, 1722, and 1760 cm^{-1} for the double bond and the two carbonyls respectively, and gives a negative ferric chloride test.

The crude product from treatment of 2',3'-O-methoxyethylideneadenosine (131) with pivalyl chloride/sodium iodide was isolated by simple ether extractions as a light brown solid foam. Thin layer chromatography of this mixture in a number of solvent systems showed only two poorly resolved spots. One of these consists of the 3'-iodo isomer (150), the 2'-iodo isomer (151), and the 3',4'-ene (152); the other is the furyl derivative (153). The amount of 153 present was not large, and has since been minimized by carefully controlling the reaction time. However, this compound exhibits a pale blue fluorescence when irradiated with the 2537 Å light used for evaluating chromatograms and shows up brightly. Purification of the crude mixture by chromatography on silica gel met with limited success. The product fractions containing 150, 151 and 152 were still colored, and resolution from 153 was not without some overlapping fractions. Since the resolution was difficult, a large adsorbent to nucleoside ratio (ca. 100:1) was needed. This made the separation time consuming and tedious, particularly for routine preparations of a synthetic intermediate. Fortunately it was eventually found that a colorless mixture of 150, 151, and 152, entirely free of 153, could be obtained easily and rapidly by chromatography on carbon. Adsorbent to nucleoside ratios as low as 5:2 were successfully used for this separation, which was achieved by elution first with chloroform:ethyl acetate (1:1) for 150, 151, and 152. The furyl derivative (153) was not eluted until neat chloroform was used as the eluant. Unlike the mixture obtained from silica purification which could not be crystallized at all, limited success was achieved in the latter case. The crystallization required very gradual cooling (ca. seven degrees over seven days) and vigorous stirring of an ethanol/water solution. The yield was poor and the conditions so sensitive that even this could not be achieved consistently. The most promising system of an opposite polarity was ether/pentane. Many attempts were made with this system, but even seeding with crystals obtained from ethanol/water gave only oils. A report has recently appeared on the technique of crystallization by diffusion,[157] and its successful use in this laboratory[145,158] prompted its application to the crystallization of 150. The first system attempted was the diffusion of pentane into an ether solution of 150, 151, and 152. In this case crystallization proceeded readily giving 150 completely pure and in an overall yield of 38%. A careful examination of the mother liquors now showed that some separation of the components could be effected with ether by repeated development (tlc). In the presence of 153 this separation had been obscured due to streaking of 153 coupled with its fluorescence. Silica/ether column chromatography was then used to separate the 3',4'-ene (152) from the 2'(3')-iodo isomers (150 and 151) and was even used to obtain some of the 2'-isomer by repetitive chromatography. However, the latter separation is nearly useless in any preparative sense. Although the resolution of 150 and 151 seemed hopeless, recourse to chromatography on carbon was again successful. It was found that if ethyl acetate rather than ethyl acetate:chloroform were used only the 3'-iodo (150) and 3',4'-ene (152) were eluted, leaving the

2'-iodo (151) to be eluted with ethyl acetate:chloroform. Rechromatography of some overlapping fractions was necessary for complete resolution, but this involved only a small percentage of the material.

Apart from the tremendous practical advantages of being able to carry out subsequent transformations on pure isomers rather than a mixture, particularly with the minor 2'-isomer, these separations were first used to determine the optimum reaction time. It was apparent from the formation of the 3',4'-unsaturated compound (152) that short reaction times were desirable, but it was impossible to make an accurate determination of the best time without an effective separation. The strong dependence of the products on the time of the reaction is shown in Figure 3 for a series of one millimole reactions run for 2, 4, 6, 8, and 10 minutes. As a check on the reproducibility of these results, two reactions were run for four minutes. The two minute reaction is seen, by extrapolation, to be only approximately 90% complete. This difference is apparently too small to show up in the yields of the 2'-isomer and the 3',4'-ene where the yields are smaller and the error larger. However, it is apparent that the yield of the 3'-iodo isomer decreases while that of the 3',4'-unsaturated compound increases with increasing reaction times. This is consistent with formation of the

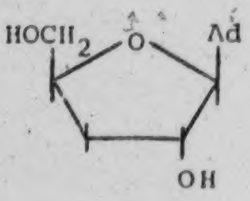
Figure 3


Percentage Yield
60
50
40
30
20
10
2
4
6
8
10
Reaction Time in Minutes
150
151
152

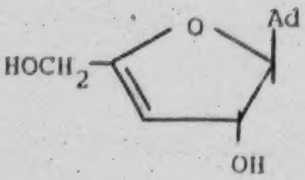
unsaturated compound from the iodo rather than via some independent route. Although it appears that the amount of the 2'-iodo isomer is invariant, this must be regarded cautiously. The amount of the furyl derivative (153) produced under these conditions was too small to be determined with any reasonable experimental error. In each case the reaction mixture was first chromatographed on a carbon column, giving the 2'-isomer in the yields shown. The mixture of 150 and 152 was then crystallized from ether/pentane, by the diffusion technique. For the four minute reactions this gave initial crystalline yields of 44 and 42% of the 3'-isomer. The mother liquors were then partially resolved on a silica column using ether to give the 3',4'-ene in 4 and 8% yields, respectively, and a mixture which was crystallized by the above procedure to give an additional 4 and 7% of 150. Assuming similar molecular weights, the mother liquors now contain only about 7 and 4% of products, and no further resolution was attempted. Thus, the first crystallization had given 92 and 86%, respectively, of the total quantity of 3'-iodo isomer which could be obtained. This is not true for the eight and ten minute reactions, which gave only 76% in the first crop. Apparently once the concentration of 150 is approximately equal to that of 152 crystallization ceases and oil is deposited. In no case has any evidence of co-crystallization been found, including the crystallization of mixtures which contained the 2'-isomer as well as the 3',4'-ene.

B. SPECIFIC SYNTHESES OF SOME DEOXY AND UNSATURATED ADENOSINE AND TUBERCIDIN DERIVATIVES

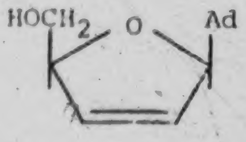
The iodo derivatives 150 and 151 have been utilized in the synthesis of deoxy and unsaturated nucleosides. The 3'-iodo-3'-deoxy-2'-O-enolester derivative (150) was converted to: 3'-deoxyadenosine (18); 3',4'-unsaturated adenosine (156); 2',3'-unsaturated adenosine (46); and the furyl derivatives (157) and (158).[114] From the 2'-iodo-2'-deoxy-3'-O-enolester compound (151), conversion to 2'-deoxyadenosine was carried out as well as the synthesis of 1',2'-unsaturated adenosine (159).[44]



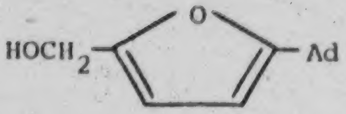
18



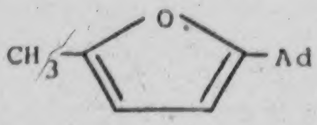
156



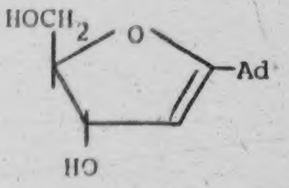
46



157



158



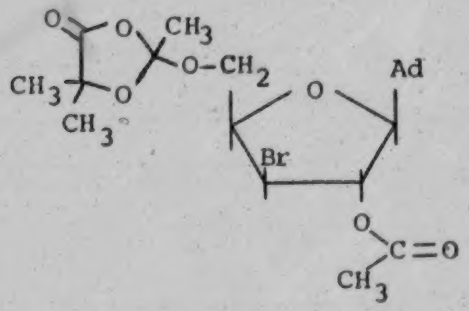
159

Although an alternate synthesis of 3',4'-unsaturated adenosine has since been reported by Moffatt,[111] no other example of a 1',2'-unsaturated purine nucleoside has been reported. The effective separation of 150 and

151 allowed these conversions to be performed specifically thus obviating subsequent chromatographic separations. In certain other transformations, separations were necessary and have been effected using Dowex 1-X2 (OH^-) ion exchange (the Dekker column[159]) or neutral silica gel column chromatography. The use of preparative tlc was restricted to preliminary investigations. The 2'-iodo isomer (151) could not be readily crystallized and was used as a chromatographically pure solid foam as obtained from the carbon column. An analytical sample was obtained by silica gel chromatography but this was neither useful nor necessary for preparative work. Transformations of 151 all gave highly crystallizable compounds so that rigorous purification was more easily effected then by simple crystallization. The corresponding derivatives of the 3'-iodo isomer (150) are not always easy to crystallize; however, since 150 was obtained analytically pure and the transformations were quite mild, no problems were encountered in this regard. This reversal of crystallizability has obviously proved to be quite advantageous.

Both the 2'-iodo and 3'-iodo isomers were readily hydrogenolyzed to the corresponding deoxy derivatives without side reactions. The 3'-deoxy-2'-O-enolester compound (155), while free of any trace of impurity, proved difficult to crystallize and was handled as a white solid foam. However, the 2'-deoxy-3'-O-enolester derivative proved to be very insoluble in alcohol and ether and was obtained in a pure, crystalline yield of 75%. In fact, these two isomers were separated by fractional crystallization in an early experiment, before methods for the separation of 150 and 151 had been devised. Deblocking in each case was effected with methanol:triethylamine:water (45:10:45) and gave crystalline yields of 87 and 90% of 2'- and 3'-deoxyadenosine, respectively. In this way the product could be isolated simply by evaporation and crystallization whereas desalting on the Dekker column[159] was necessary if sodium alkoxide were used. The overall yield to 3'-deoxyadenosine (18) from 2',3'-O-methoxyethylideneadenosine (131) was 44%.

Of the other methods for preparing 18 discussed earlier, that used by Moffatt and coworkers[109] is nearest to the present procedure both in basic approach and in yield. These workers obtained a 33% yield of 6-amino-9-[3-bromo-3-deoxy-2-O-acetyl-5-O-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]purine (160) from the reaction of α-acetoxyisobutyryl bromide with adenosine by crystallization of the crude reaction mixture. Partial purification of the mother liquors and nmr evaluation suggested that they contained an additional 44% of a 3:2 mixture of 160 and the 2'-bromo isomer. However, the isomers apparently could not be resolved and the only reported use of this mixture has been in preparing 2',3'-anhydroadenosine. A further drawback was noted during hydrogenolysis of 160.

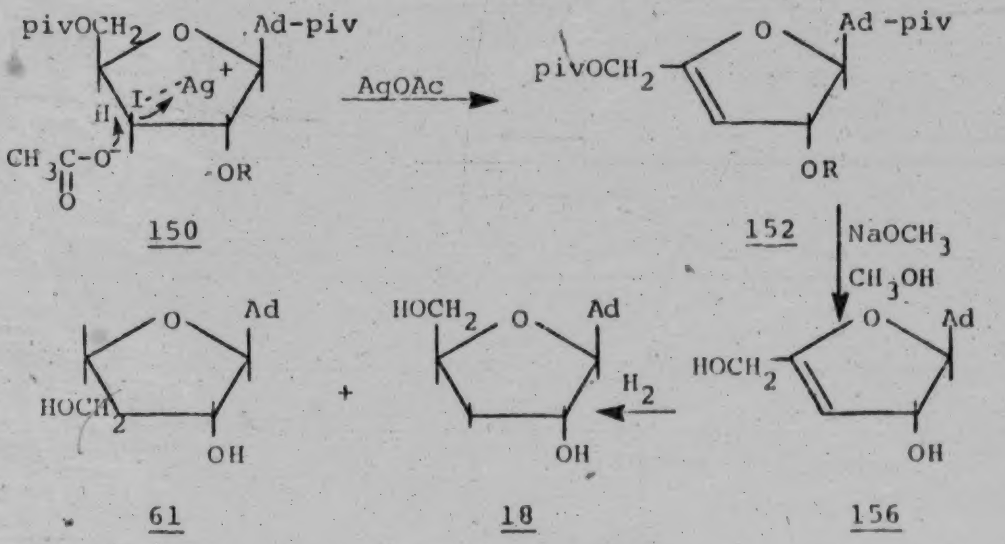


160

Apparently partial 2',3' elimination of acetoxy and bromo functions occurred to give a 2',3'-unsaturated derivative. Concomitant hydrogenation of this material gave the expected 3'-deoxyadenosine (18) contaminated with an approximately equal amount of 2',3'-dideoxyadenosine (20). The only method devised by these authors to avoid this elimination was the removal of the 2'-O-acetyl group although this could not be done selectively. Complete deblocking of 160 was effected in 73% yield by treatment with methanolic hydrochloric acid, an eight day procedure. Hydrogenolysis of this material could now be carried out in 78% yield, for a 19% overall yield of 3'-deoxyadenosine (18).

Since some of the 3',4'-unsaturated-2'-O-enolester derivative (152) was formed from the 3'-iodo isomer 150 during its preparation in our original reaction mixture, the use of refluxing pyridine to effect conversion of 150 to 152 was investigated. Unfortunately a further elimination to the furyl compound (153) occurred as well, making it impossible to obtain 152 in high yield. Separation of the 3',4'-ene (152) from 153 with the carbon column was very easy, but a more specific synthesis of 152 was sought. The use of 1,5-diazabicyclo-[4.3.0]-nonene-5 (DBN) in pyridine solution at or below room temperature still gave significant amounts of 153, although less than did refluxing pyridine. A pyridine solution of silver acetate was found to be a more selective reagent. Treatment of 150 for ca. 17 hours at room temperature gave 152 in quantitative yield, pure by tlc (silica, ether), and crystallization of 152 from ether/pentane by the diffusion method gave a first crop yield of 84%. Even using the diffusion method, crystallization of 152 only proceeds in high yield when it is already quite pure. Attempted hydrogenation of this blocked 3',4'-unsaturated compound (152) gave complex mixtures, apparently as the result of competing allylic ester hydrogenolysis. Even furyl derivatives were observed by tlc in these reduction mixtures and this approach was not pursued further.

Deblocking of 152 to 6-amino-9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)purine (156)[114] was effected both with the methanol:triethylamine:water system and with sodium methoxide in methanol. The product is highly insoluble in water allowing yields of 87 and 92%, respectively, to be obtained by direct crystallization. Because of the low solubility of 156, it was not necessary to desalt the solution before crystallization. It was mentioned earlier that the corresponding 5'-carboxylic acid ester and aldehyde derivatives of 156 are known.[92,94]



Scheme XXXII

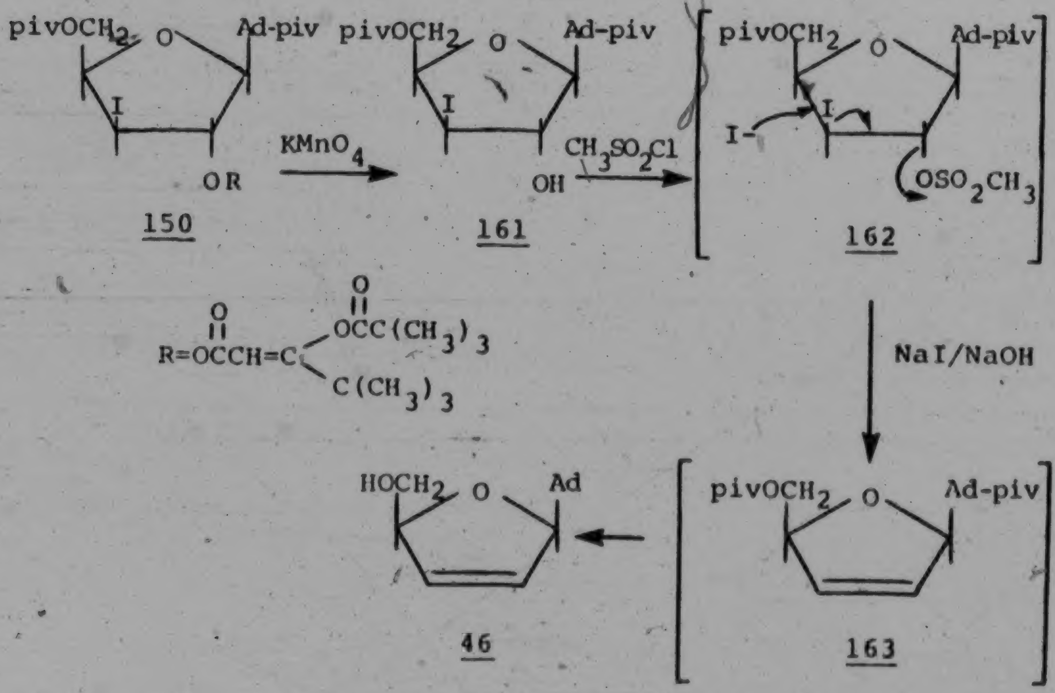
However, until very recently no other synthesis of 156 itself had been reported. This alternate synthesis, by Moffatt and coworkers, was effected by treatment of the

3'-bromo-2'-O-acetyl derivative (160) with DBN at 80°.[111] Apparently further elimination to a furyl derivative was not a problem here, although an undetermined amount of 2',3'-unsaturated adenosine was reportedly formed. The yield from 160 was 59%, for an overall yield of 19%.[111] The present procedure, with an overall yield of 45%, compares favorably with this approach.

Reduction of the 3',4'-ene was effected using 10% palladium on carbon and gave a mixture of the 4'-epimers, 3'-deoxyadenosine (18) and 6-amino-9-(3-deoxy-α-L-*threo*-pentofuranosyl)purine (61). These compounds were readily separated on a Dekker column,[159] giving 18 in 53% and 61 in 35% yields. This ratio of 1.5:1 is identical to that reported by Nagpal and Horwitz who had obtained the same compounds by reduction of the methyl ester of 3',4'-unsaturated-adenosine-5'-carboxylic acid. The latter route gives the two 4'-epimers in yields of 22 and 14% from methyl 9-(2,3-O-isopropylidene-β-D-ribofuranosyluronate)adenine. The overall yields from 131 by the present route are 24 and 16%.

Although formation of the "enolester" rather than a simple acetyl ester initially presented some problems in characterization, this "bizarre" function (as it has been recently described[111]) has proved to be highly useful. Attempted deblocking of the iodo-enolesters (150) and (151) under a variety of both acidic and basic conditions was not satisfactory. Reaction with zinc chloride gave mixtures of partially deblocked material,[143] and treatment with 80% acetic acid only removed the 6-*N*-pivalyl group. Usual basic conditions resulted in formation of the 2',3'-epoxide before removing either 5'-*O*- or 6-*N*-pivalyl groups.[143] However, mild treatment with potassium permanganate was found to selectively remove the enolester function in high yield. Selective deblocking of the 2'- or 3'-hydroxyl has not been reported for the adenosine and tubercidin compounds obtained from reaction with α-acetoxyisobutyryl halides. In the present case the syntheses of both 6-amino-9-(2,3-dideoxy-β-*D*-*glycero*-pent-2-enofuranosyl)purine (46) (2',3'-unsaturated adenosine) and of 6-amino-9-(2-deoxy-*D*-*erythro*-pent-1-enofuranosyl)purine (159) (1',2'-unsaturated adenosine) have made use of this selective removal. The reaction was conveniently carried out in aqueous pyridine in an ice bath at about 2° for two hours. Isolation of the product was achieved by simple extraction and crystallization. In this way 6-*N*-pivalamido-9-(3-iodo-3-deoxy-5-O-pivalyl-β-D-xylofuranosyl)purine (161) was obtained in quantitative yield, pure by tlc. Crystallization of this material from ether gave an 86% yield of 161 in two crops. Similarly, 6-*N*-pivalamido-9-(2-iodo-2-deoxy-5-*O*-pivalyl-β-*D*-arabinofuranosyl)purine (164) was obtained in a crystalline yield of 75%. While a high recovery crystallization of 161 is possible only when it is already pure, the 2'-iodo-3'-hydroxy isomer (164) is readily crystallized from even complex mixtures. In some early work, the permanganate reaction was carried out on mixtures of both of the iodo isomers as well as some of the 3',4'-ene (152), which was shown to be converted to 6-N-pivalyladenine under these conditions. After extraction of the bulk of the pivalyl adenine into water, most of the 2'-isomer (164), which remained in the ethyl acetate layer, could be crystallized. However, isolation of both isomers 161 and 164 in good yield required careful silica gel chromatography, making it a decidedly inferior route. The selective deblocking of 150 and 151 to give 161 and 164 was obvious from the absence in the nmr of the vinyl proton resonance and two of the t-butyl resonances. The uv maxima were still at 272 nm and the mass spectra showed parent peaks at m/e 545 consistent with loss of the enolester function.

The transformation of trans halohydrins to the corresponding unsaturated derivatives with phosphorous oxychloride in pyridine was recently reported.[160] Unfortunately, attempted application of this procedure to conversion of the 3'-iodo-2'-hydroxy isomer (161) to the blocked 2',3'-unsaturated compound (163) gave only pivalyl adenine. Even pyridine hydrochloride at 0° is apparently too acidic for 163. A more satisfactory approach was found in mesylation of the 2'-hydroxyl followed by sodium iodide in acetone catalyzed elimination[50] to 163. However, some formation of pivalyl adenine occurred under these conditions as well. The 3'-iodo-2'-O-mesyl intermediate (162) was identified by the methyl resonance in the nmr at δ 3.33, the ir absorption at 1175 cm^{-1} ($-OSO_2-R$), and the uv maximum at 272 nm. This compound was too unstable to completely purify and characterize. Therefore conversion of 161 to 2',3'-unsaturated adenosine was most conveniently carried out without isolation of either the 2'-iodo-3'-O-mesyl (162) or the blocked unsaturated compound 163.



Scheme XXXIII

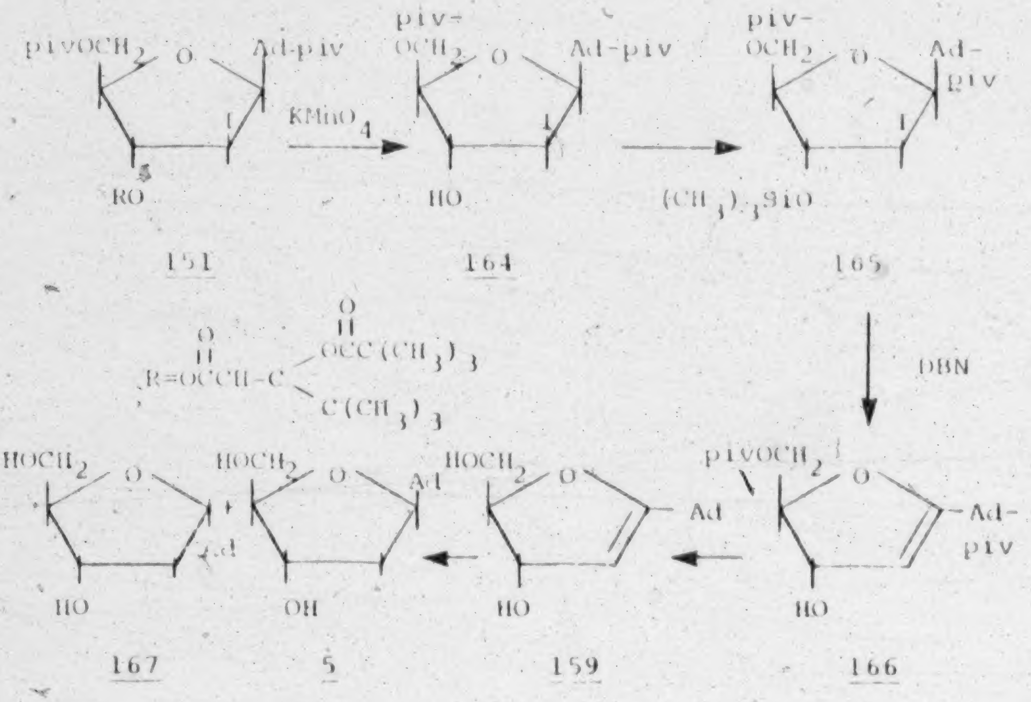
Treatment of 161 with methanesulfonyl chloride in pyridine at 2° was followed by addition of an aqueous solution of sodium hydroxide and sodium iodide. A red color immediately appeared, which slowly dissipated as the iodine produced in the elimination was converted to hypoiodite, leaving a pale yellow solution. By following this procedure, only one spot could be detected on tlc of the crude reaction mixture (silica; 5% methanol in ether). The solution was desalted on a Dekker column[159] and gave 2',3'-unsaturated adenosine in 89% yield, for an overall yield of 44% from 131.

This compound, 46, had earlier been prepared from 2'-deoxyadenosine in 41% yield by McCarthy et al.,[81] and more recently by Moffatt and coworkers.[111] The latter synthesis involves treatment of the 3'-bromo derivative (160) with chromous acetate and ethylenediamine at -78° under an argon atmosphere. The inability to selectively deblock the 2'-hydroxyl would prevent use of the more convenient mesylation/elimination approach with 160. The chromous acetate used by Moffatt[111] was prepared in an argon-filled drybox by treating chromium metal with 70% perchloric acid (deoxygenated) for 60 hours followed by addition of the resulting blue solution to a deoxygenated aqueous solution of sodium acetate. Treatment of the crystalline 3'-bromo-2'-O-acetyl derivative (160) with chromous acetate gave 59% of 2',3'-unsaturated adenosine (46) for an overall yield of 20%, as well as 30% of 3'-deoxyadenosine (18). The 3'-iodo-2'-O-acetyl compound (analogous to 160) was prepared by reaction of α-acetoxyisobutyryl chloride in the presence of excess sodium iodide.[111] Only a portion of the crude mixture was purified by repeated preparative tlc followed by crystallization to give the 3'-iodo isomer in what would correspond to 38% yield if the entire crude mixture were so purified. The only reaction of the iodo compound described was treatment of the crude mixture with chromous acetate. This gave 48% of 46, 9% of 18 and 7% of 3',4'-unsaturated adenosine (156). The crude product from preparation of the 3'-chloro-2'-O-acetyl compound (analogous to 160), was similarly treated and gave 62% of 46, 10% of 18, and 6% of 156. It is not possible to determine the overall yield in the latter case since the published figures for the crude yield of chloro derivatives correspond to 106%, allegedly a 9:1 mixture of 3':2'-chloro, plus 21% of adenine (127% total yield). The pure 3'-chloro isomer was crystallized in 20% yield, but reactions with the pure compound are not reported.

The only example of a 1',2'-unsaturated nucleoside which has previously been noted is 1-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)uracil.[161] The evidence in support of this assignment rests solely on the uv spectrum, qualitative color tests, and paper chromatography. Since the 2'-iodo-3'-O-enolester isomer (151) could be readily obtained in a nearly pure state in 16% yield, the synthesis of 1',2'-unsaturated adenosine was attempted. Initial efforts using silver acetate in pyridine, analogous to the preparation of 3',4'-unsaturated adenosine, were unsuccessful. Apparently the desired product underwent an additional elimination to the furyl derivative (153) as rapidly as it was formed. Treatment of the 2'-iodo-3'-hydroxy compound (164), obtained by permanganate deblocking of 151, was only partially successful, owing to concomitant epoxide formation. The synthesis of 1',2'-unsaturated adenosine (159) in high yield was achieved by blocking the 3'-hydroxyl of 164 with a trimethylsilyl group. Although the 2'-iodo-3'-O-trimethylsilyl derivative (165) was stable enough to be isolated and purified by chromatography on silica, the synthesis was more conveniently carried out without isolation of intermediates. Thus, N-O-bis(trimethylsilyl)acetamide was added to a pyridine solution of 164, and after 3'-O blocking was complete as judged by tlc, (silica, 10% methanol in ether) DBN was added to effect elimination. After elimination was completed the trimethylsilyl group was rapidly cleaved upon addition of methanol in the presence of the strongly basic DBN, and 6-N-pivalamido-9-(2-deoxy-5-O-pivalyl-D-*erythro*-pent-1-enofuranosyl)purine (166) was isolated as a gel. This compound could not be crystallized, but was smoothly deblocked with sodium methoxide to give 159 which is very insoluble in alcohol and water and was obtained in crystalline yields of from 84 to 89%. The overall yield from 131, however, was a modest 10-11%. The 1',2'-unsaturated adenosine is unstable to acid, giving adenine quantitatively on attempted determination of the uv spectrum in 0.1N HCl. Thermally, 159 decomposed to 9-(5-hydroxymethyl-2-furyl)adenine (157). This decomposition to 157 was detectable on drying 159 at 64° for 24 hours. Like the furyl compound (157), 159 has a blue fluorescent appearance when observed under the 2537 Å light commonly employed for evaluating thin layer chromatograms. This similarity with the furyl derivative also appears in the position of the uv maximum which is shifted hypsochromically from the normal adenosine position of 259 nm to 251 nm for 159 and to 249 nm for 157.

The double bond of 1',2'-unsaturated adenosine was readily reduced to give 2'-deoxyadenosine (5) and 6-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine (167). In addition, some hydrogenolysis of the glycosidic linkage occurred. Separation on a Dekker column[159] gave

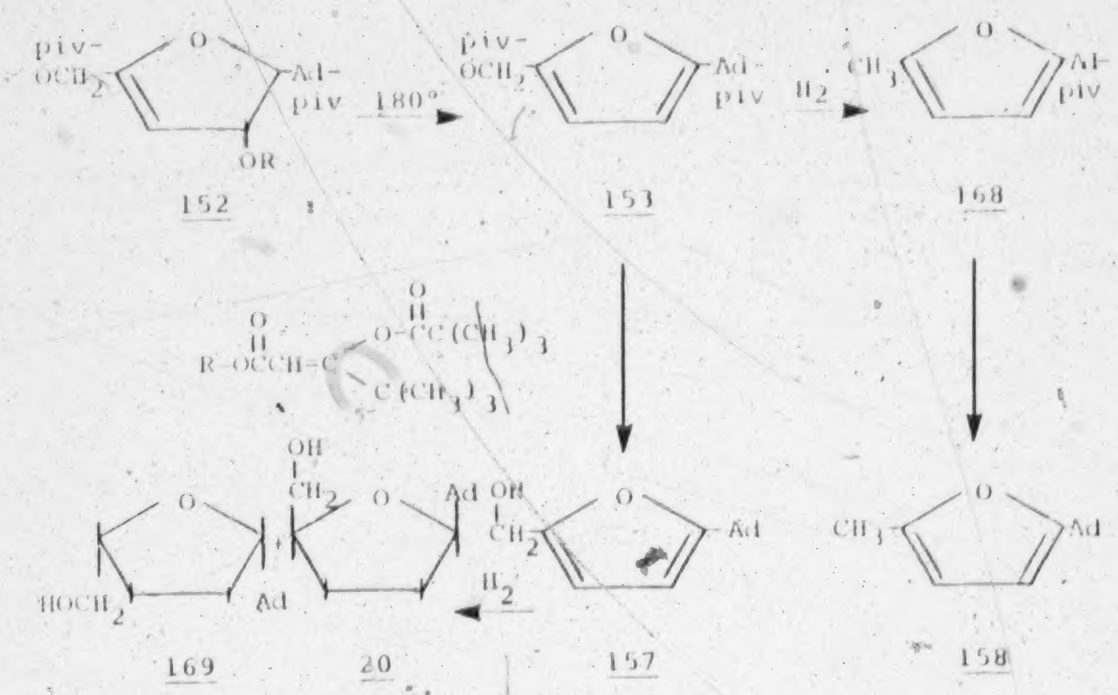
14% of 167 and 68% of 5. The required amount of adenine, 18% (by uv), was eluted with 0.1 M ammonium bicarbonate.



Scheme XXXIV

Reduction of the blocked compound (166) appeared to give no α-anomer and an increased amount of hydrogenolysis. The β-anomer was identical with that prepared above and the α-anomer with that prepared previously by Robins and Robins via a coupling procedure.[162] Thus, this sequence demonstrates a route for conversion of an intact ribonucleoside to its 2'-deoxy-α-D-anomer. However, it should be recognized that at an overall yield of about 1.5% this route to 2'-deoxy-α-D nucleosides is not very useful in a synthetic sense, at least for compounds which are accessible by coupling procedures.

Although the thermal instability of the 3',4'-unsaturated derivatives (152 and 156) is not as great as for the 1',2'-unsaturated derivatives it has not been possible to obtain a mass spectrum of 152, because of its decomposition to 153. This was also true of 159 and 166 which had to be trimethylsilylated to obtain a parent peak. Conversion of 152 to 6-N-pivalamido-9-(5-pivaloxymethyl-2-furanyl)purine (153) proceeded readily at 180° and was complete in three minutes giving a crystalline yield of 76%. Hydrogenolysis of 153 to 6-N-pivalamido-9-(5-methyl-2-furanyl)purine (168) was effected in 82% yield. Deblocking with methanol:triethylamine:water, followed by crystallization from methanol gave 6-amino-9-(5-methyl-2-furanyl)purine (158)[81] in 88% yield. Alternatively, 153 could be deblocked with methanolic sodium methoxide to give 92% of the highly insoluble, 6-amino-9-(5-hydroxymethyl-2-furanyl)purine (157). Reduction of 157 to racemic 2',3'-dideoxyadenosine (20 and 169) could now be effected in 64% yield. This product had identical nmr and mass spectra with those of 2',3'-dideoxyadenosine (20) prepared by hydrogenation of 2',3'-unsaturated adenosine.[81]



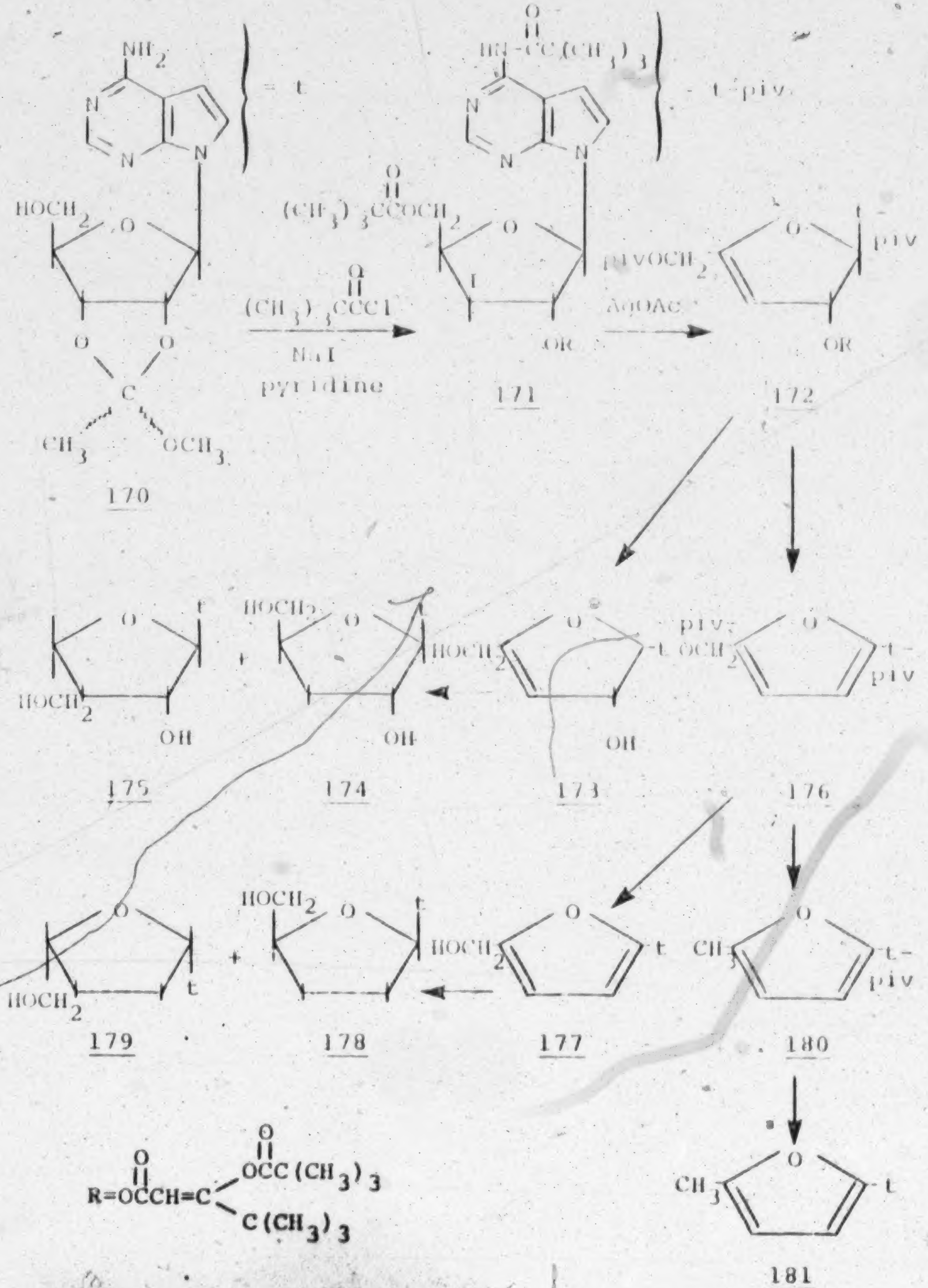
Scheme XXXV

The 1',4'-*cis* configuration was further confirmed by 5'-*O* tosylation and N^3 → 5'-cyclonucleoside formation. The exclusive β-*D*, *L* configuration is not surprising since electrophilic addition to furans is known to proceed via *cis* 1,4-addition, and approach to a catalytic surface is usually *cis* specific.

Many of these transformations have also been carried out on the nucleoside antibiotic tubercidin. Preparation of 2',3'-*O*-methoxyethylidenetubercidin (170) proceeded analogously to the adenosine compound in near quantitative yield.[143] Reaction of 170 with pivalyl chloride and excess sodium iodide as above gave only 4-*N*-pivalamido-7-[3-iodo-3-deoxy-5-*O*-pivalyl-2-*O*-(4,4-dimethyl-3-pivaloxypent-2-enoyl)-β-D-xylofuranosyl]pyrrolo[2,3-*d*]pyrimidine (171). None of the 2'-iodo isomer was found. This is consistent with results obtained when tubercidin was reacted with α-acetoxyisobutyryl halides.[106,107] In the present case there also appears to be less tendency for the initially formed 3'-iodo-2'-*O*-enolester compound (171) to undergo elimination of hydrogen iodide to the 3',4' unsaturated derivative (172). Simple solvent extraction of the product and purification on a carbon column similar to that described earlier for the adenosine case gave 171 in 64% yield, containing only a trace of 172. Unfortunately, neither of these compounds were obtained in crystalline form and were handled as white, solid foams. Tubercidin compounds seem generally to be considerably more difficult to crystallize than the analogous adenosine compounds. The maximum absorption in the uv spectra of 171 and 172 was shifted bathochromically to 287 from 269 nm and the nmr and mass spectra were analogous to the corresponding adenosine compounds (150 and 152).

Treatment of 171 with silver acetate gave smooth elimination to 4-*N*-pivalamido-7-[3-deoxy-5-*O*-pivalyl-2-*O*-(4,4-dimethyl-3-pivaloxypent-2-enoyl)-β-D-*glycero*-pent-3-enofuranosyl]pyrrolo[2,3-*d*]pyrimidine

(172) in quantitative yield.



Scheme XXXVI

Deblocking was effected with methanolic sodium methoxide to give 4-amino-7-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl]pyrrolo[2,3-*d*]pyrimidine (**173**). However, in this case it was necessary to purify the crude product on a Dekker column[159], and the yield was only 75%, for an overall yield of 48% from **170**. Like 3',4'-unsaturated adenosine[$[\alpha]_{D}^{24°}$ −354° (*c* 0.39, DMF:water, 1:1)], this compound (**173**) has a very large negative optical rotation: $[\alpha]_{D}^{24°}$ −457° (*c* 0.98, DMF).

Reduction of **173** under the same conditions used for **159** followed by separation on the Dekker column[159] gave 3'-deoxytubercidin (**174**) and its 4'-epimer, 4-amino-7-(3-deoxy-α-*L*-*threo*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**175**). However, the isomer yields in this case were reversed. A 38% yield of the β-*D*-anomer and 53% yield of the α-*L*-anomer was obtained. This is a ratio of 1:1.4, while for the adenosine compounds the ratio was 1.5:1. There seems to be no apparent explanation for this dramatic reversal. The identity of the 4'-epimers was determined by comparison of **174** to 3'-deoxytubercidin[106] and can also be deduced from the nmr and mass spectra.

Preparation of 4-N-pivalamido-7-(5-pivaloxymethyl-2-furanyl)pyrrolo[2,3-*d*]pyrimidine (**176**) was effected by heating **172** at 180° for two minutes and gave a crystalline yield of 70% of **176**. Hydrogenolysis of **176** to 4-N-pivalamido-7-(5-methyl-2-furanyl)pyrrolo[2,3-d]pyrimidine (180) proceeded in 82% yield. Deblocking of 176 and 180 by the methods used for the analogous adenosine compounds gave 4-amino-7-(5-hydroxymethyl-2-furanyl)pyrrolo[2,3-d]pyrimidine (177) and 4-amino-7-(5-methyl-2-furanyl)pyrrolo[2,3-d]pyrimidine (181) in yields of 91% and 94%, respectively. Hydrogenation of 177 to racemic 2',3'-dideoxytubercidin (178 and 179) proceeded in 77% yield. The 1',4'-*cis* configuration was confirmed by $N^1 \rightarrow 5'$-cyclonucleoside formation, but it was also apparent from examination of the nmr and mass spectra as will be discussed in the following section.

C. SOME REPRESENTATIVE NMR AND MASS SPECTRA

In the nmr spectra of the chloro-acetyl (134) and chloro-enolester (141) compounds (Figures 1 and 2), only the 3'-chloro isomer can be seen. Since the iodo isomers (150 and 151) were separated, their spectra as well as the spectra of the deoxy derivatives (154 and 182) and the 3'-iodo-2'-O-enolester tubercidin compound (171) are shown in Figures 4 to 8. A first order analysis of the nmr spectrum of each compound prepared in this work is given in detail in the appropriate experimental description and the assignments and couplings will be found there. From comparison of the chloro compounds (Figures 1 and 2) it appears that the most downfield (ca. δ 1.41) and most upfield (ca. δ 1.17) of the t-butyl resonances are likely to be the 6-N-pivalyl and the vinyl t-butyl, respectively. The spectrum of ethyl 4,4-dimethyl-3-pivaloxypent-2-enoate, (155, Figure 9) with signals at δ 1.13 and 1.34 supports this as does the spectrum of the pivalylketene acetal (138, Figure 10) with signals at δ 1.11, 1.15, and 1.38. In this case the vinyl proton also shows an upfield shift to δ 5.27 from the "enolester" position of δ 5.75. The nmr of the 2'-iodo-3'-O-trimethylsilyl derivative (165) with signals at δ 1.37 and 1.41 also supports the above assignment. Finally, treatment of 150, for example,

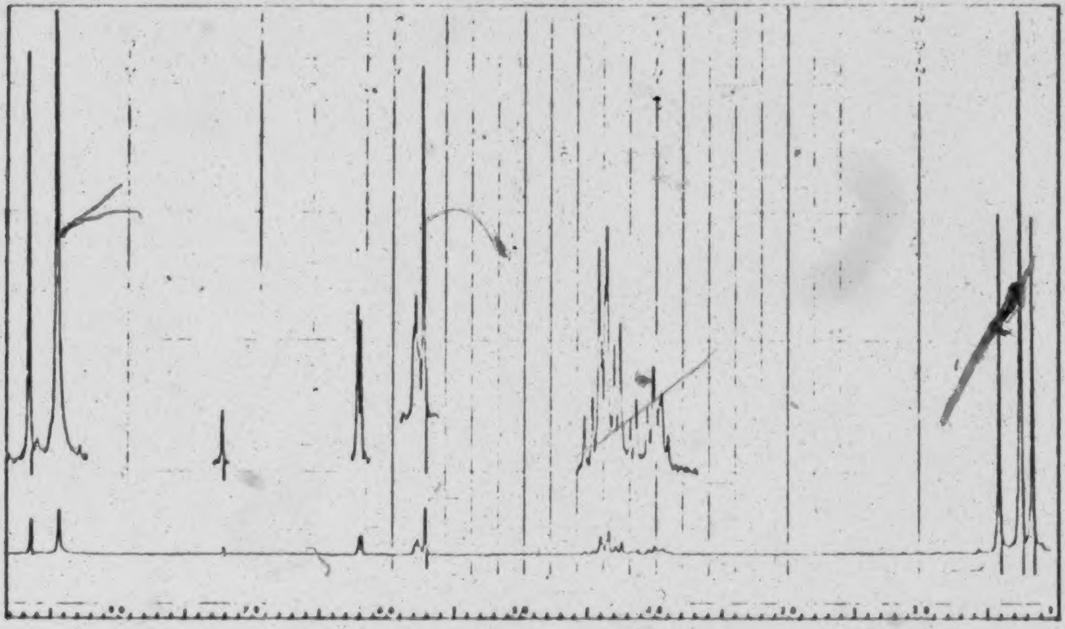


Fig. 4. 6-N-Pivalamido-9-(3-iodo-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)-purine (150) (CDCl$_3$).

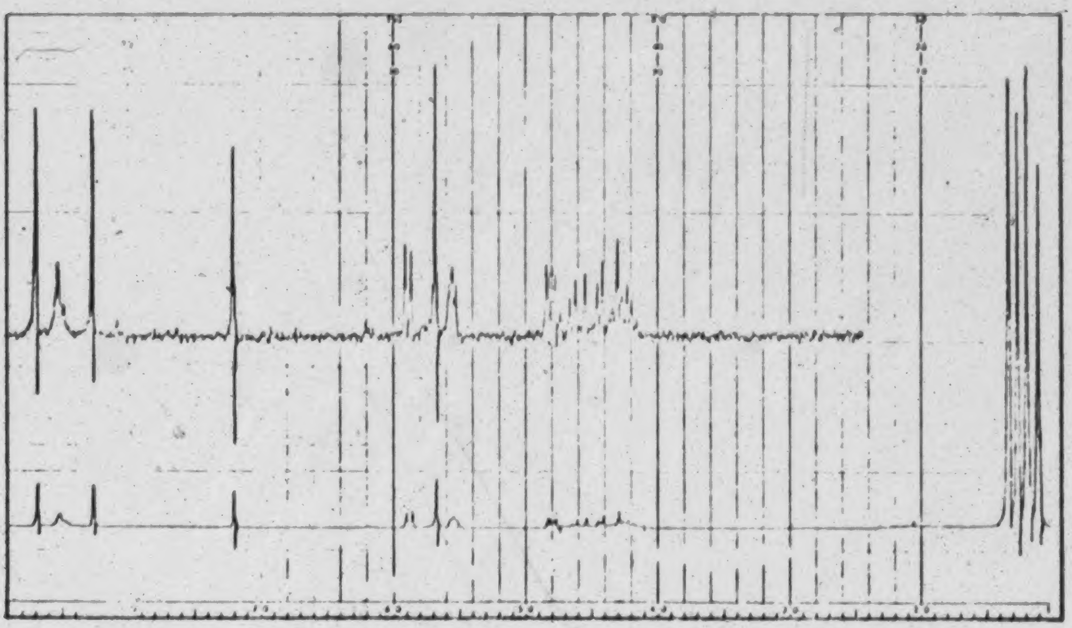


Fig. 5. 6-N-Pivalamido-9-(2-iodo-2-deoxy-5-O-pivalyl-3-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-arabinofuranosyl)-purine (151) (CDCl$_3$).

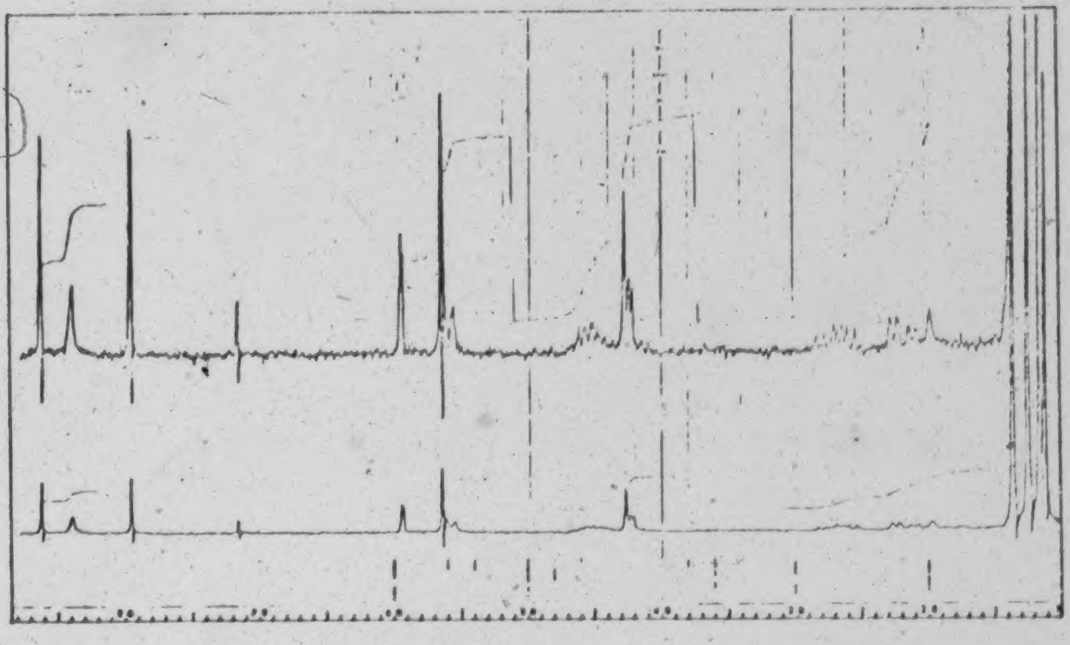


Fig. 6. 6-N-Pivalamido-9-(3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-erythro-pentofuranosyl)-purine (155) ($CDCl_3$).

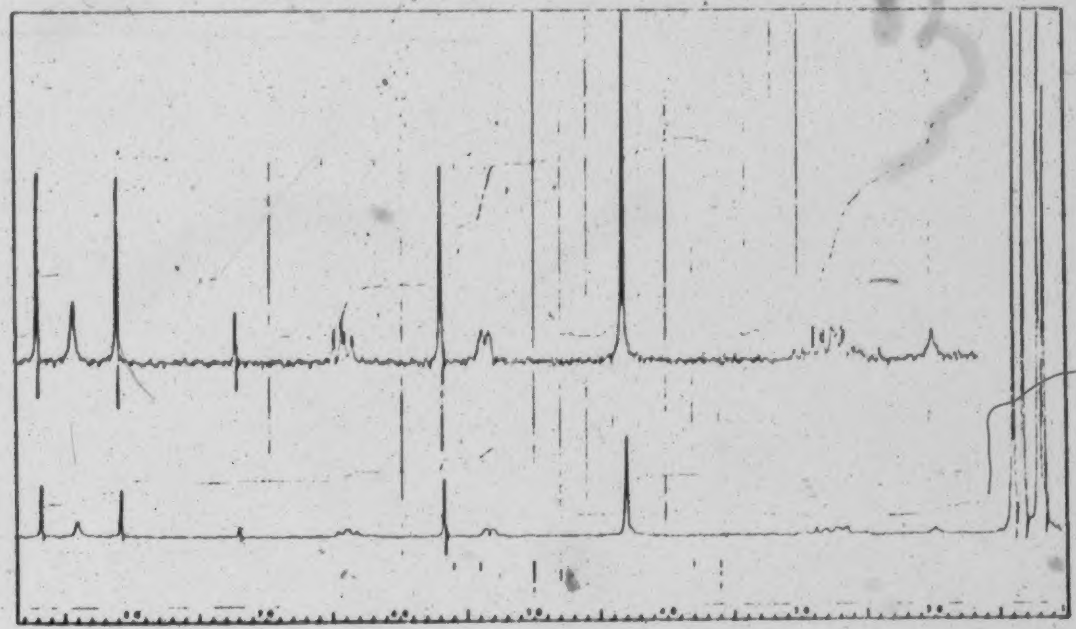


Fig. 7. 6-N-Pivalamido-9-(2-deoxy-5-O-pivalyl-3-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-erythro-pentofuranosyl)-purine (182) ($CDCl_3$).

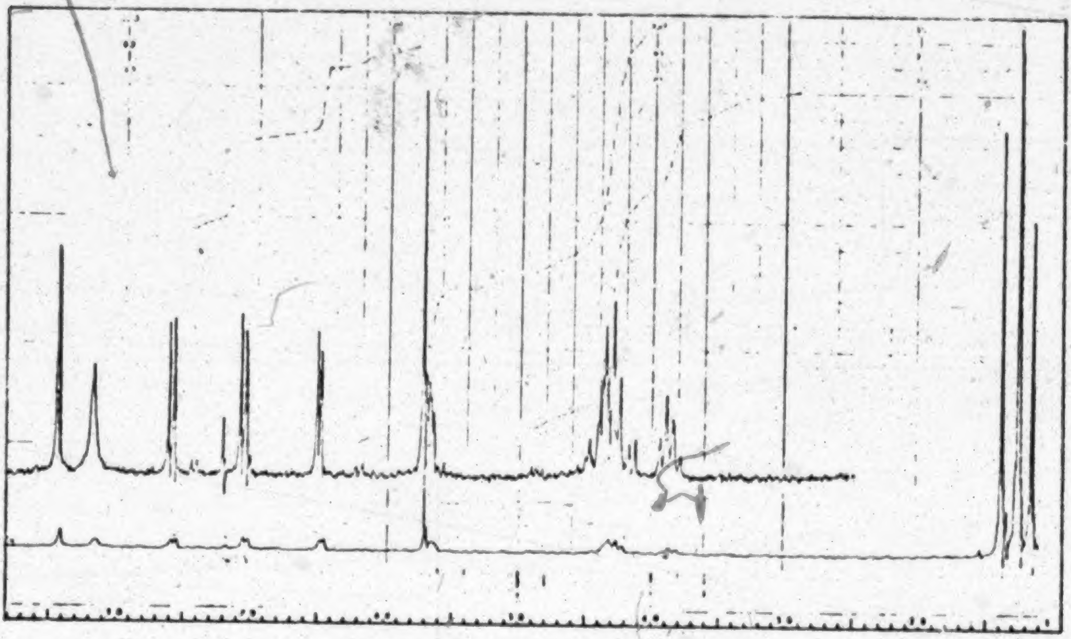


Fig. 8. 4-N-Pivalamido-7-(3-iodo-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)-pyrrolo[2,3-d]pyrimidine (171) ($CDCl_3$).

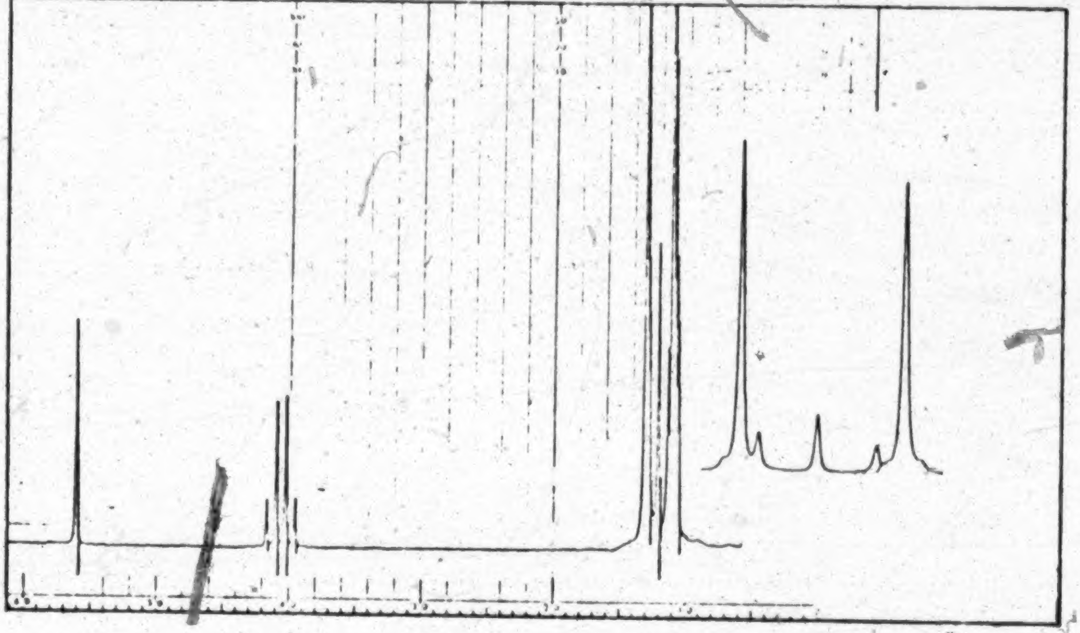


Fig. 9. Ethyl 4,4-Dimethyl-3-pivaloxypent-2-enoate (154) ($CDCl_3$).

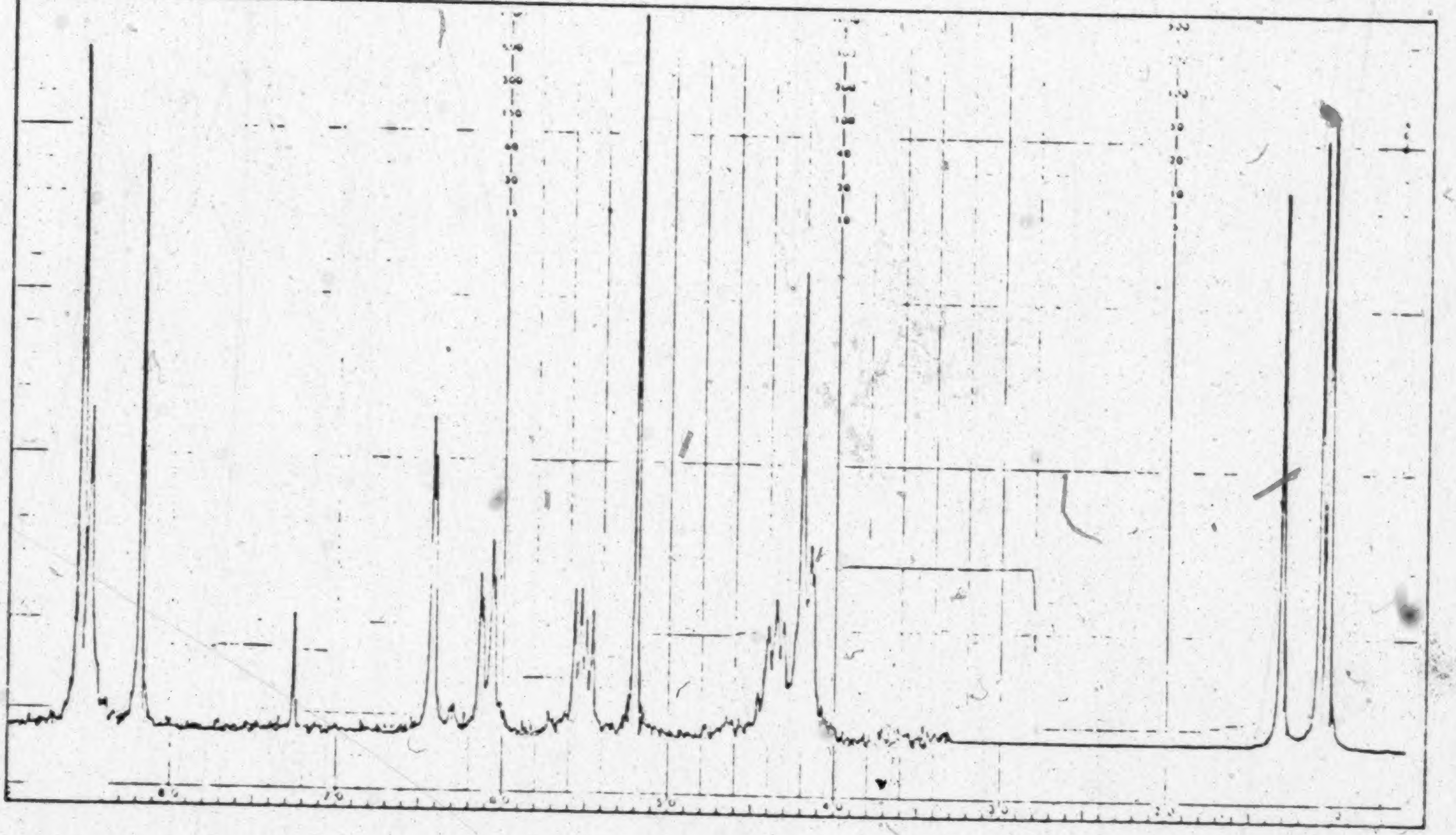


Fig. 10. 6-N-Pivalamido-9-(2,3-O-[4,4-dimethyl-3-oxo-pent-1-enylidene]-5-O-pivalyl-β-D-ribofuranosyl)purine (138) ($CDCl_3$).

with 80% acetic acid removes the 6-N-pivalyl group, as shown by the hypsochromic shift in the uv maximum from 272 nm to 260 nm. In this case the resonance at δ 1.41 is absent.

Mass spectral analysis was originally the most important tool in elucidation of the "enolester" structure. This function has a strong, characteristic fragmentation which appears in all of its derivatives. The mass spectra of methyl and ethyl (154) 4,4-dimethyl-3-pivaloxypent-2-enoate (Figures 11 and 12) illustrate this fragmentation most clearly. The methyl ester was prepared by treatment of a sample of 154 with methanolic sodium methoxide. Comparison of the two spectra allows many assignments to be made with confidence since those fragments which have lost the methyl or ethyl group have the same mass while those which have not differ by 14. Surprisingly, there is no peak corresponding to loss of 85 [$(CH_3)_3CCO$] from the parent peak, but instead only loss of 84 (ion d). A fragmentation pattern which is consistent with the spectra obtained is shown in Scheme XXXVII. For these two compounds the fact that ions c (199/185), d (172/158), h (115/101), and i (87/73) contain the alkyl residue is confirmed by their difference in mass (14). Ions a (211), e (127), f (85) and b (57) are seen to have lost the alkyl group, since they have the same mass. The formation

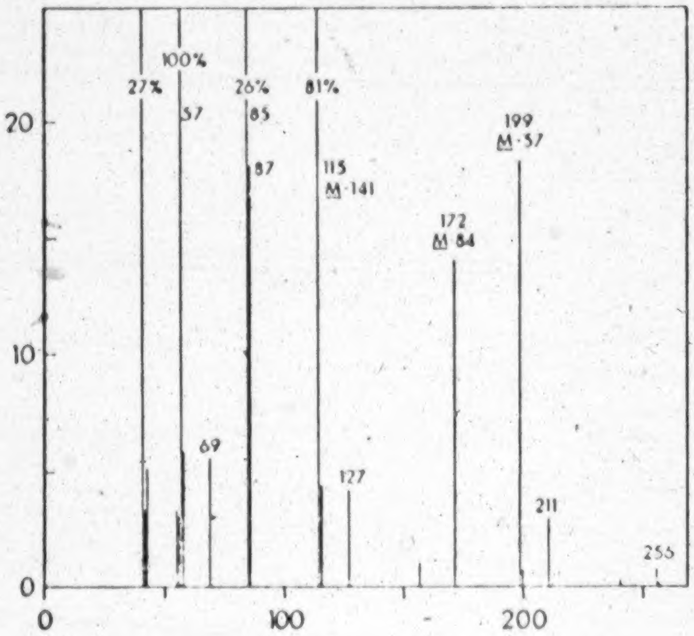


Fig. 11. Ethyl 4,4-Dimethyl-3-pivaloxypent-2-enoate (154).

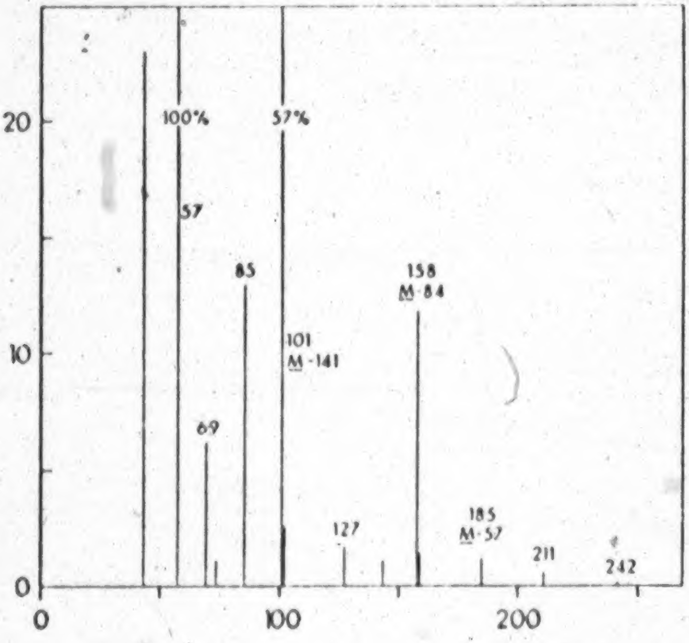
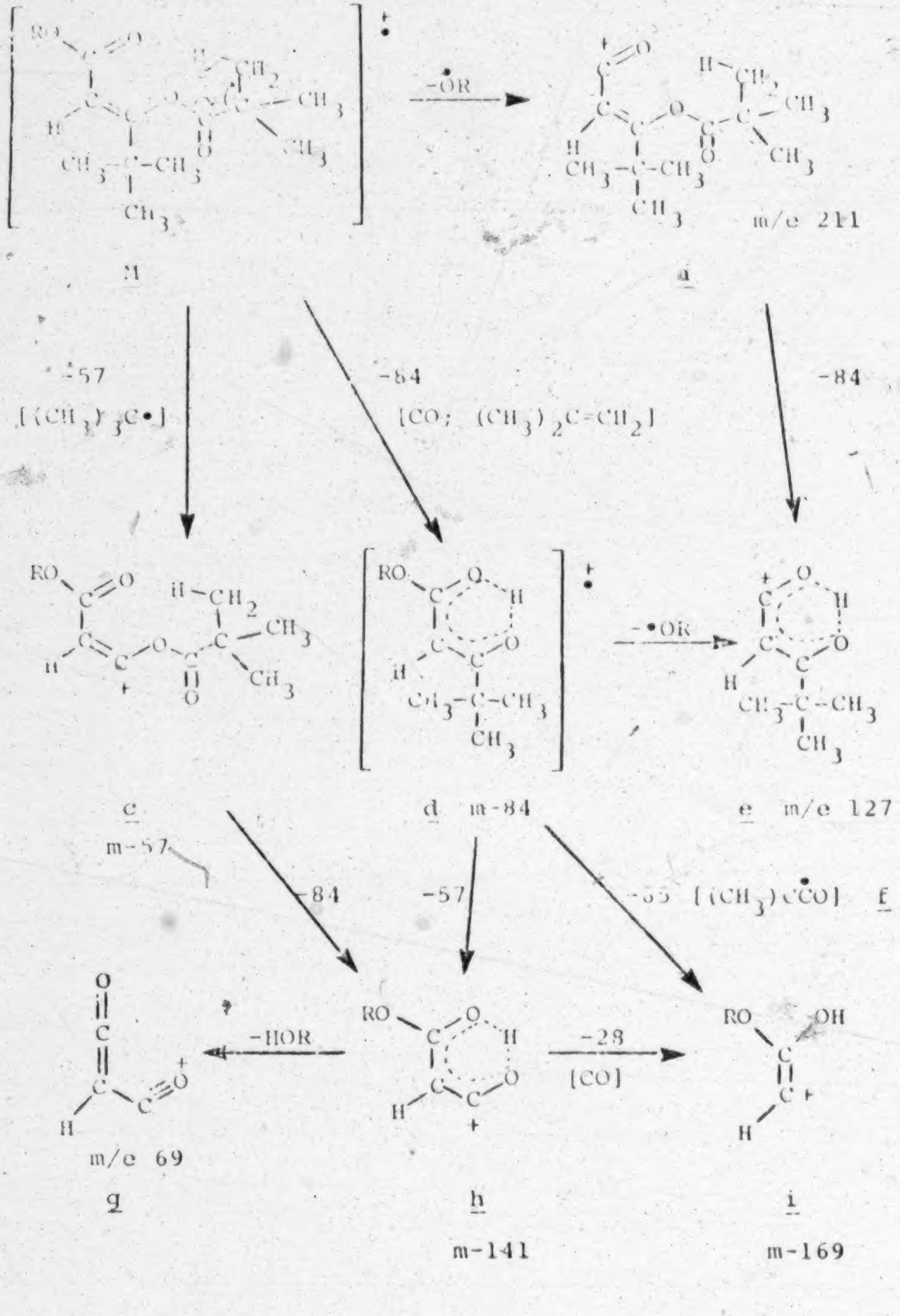


Fig. 12. Methyl 4,4-Dimethyl-3-pivaloxypent-2-enoate.



Scheme XXXVII

of ion h (115) in the spectrum of 155 is supported by metastable peaks at 66 and 77, which correspond to fragmentation of ion c (199) to ion h, and ion d (172) to ion h, respectively. A similar fragmentation has been reported for some β-keto ester compounds in which ions h and g were produced as well as ions analogous to d and e.[163]

A comparison of the spectra of the chloro-acetyl (134) and chloro-enolester (141) compounds further illustrates the diagnostic value of the above fragmentation, when R (Scheme XXXVII) is a nucleoside. The spectrum of 141 (Figure 13) shows major peaks at m/e: 606 (c), 522 (h), 304 (base+pivalyl+H, ion j), 303 (loss of base+H from h, ion k), 220 (base+2H, ion l), and lesser peaks at m/e: 579 (d), 578 (M-85, $(CH_3)_3CCO$), 445 (the sugar fragment, M-218, ion m), 361 (loss of 84 from the sugar fragment, ion n), 211 (a), and 127 (f).* Small metastable peaks corresponding to: 663 (M) to 606 (c), at 554; 606 (c) to 522 (h), at 450; 445 (m) to 361 (n), at 292.5; and 522 (h) to 303 (k), further support Scheme XXXVII. The chloro-acetyl compound (134, Figure 14) has, instead of the enolester ions, peaks at m/e: 460 (M-^{35}Cl), 410 (M-85), 358 (loss of 102, $(CH_3)_3CCO_2H$, from 460), 277 (sugar, m) 248 (base+30, ion o)[164], and 220 (base+2H, ion l). No peaks corre-

---

* "Base" refers to the heterocyclic base of the nucleoside including any exocyclic amino substituent.

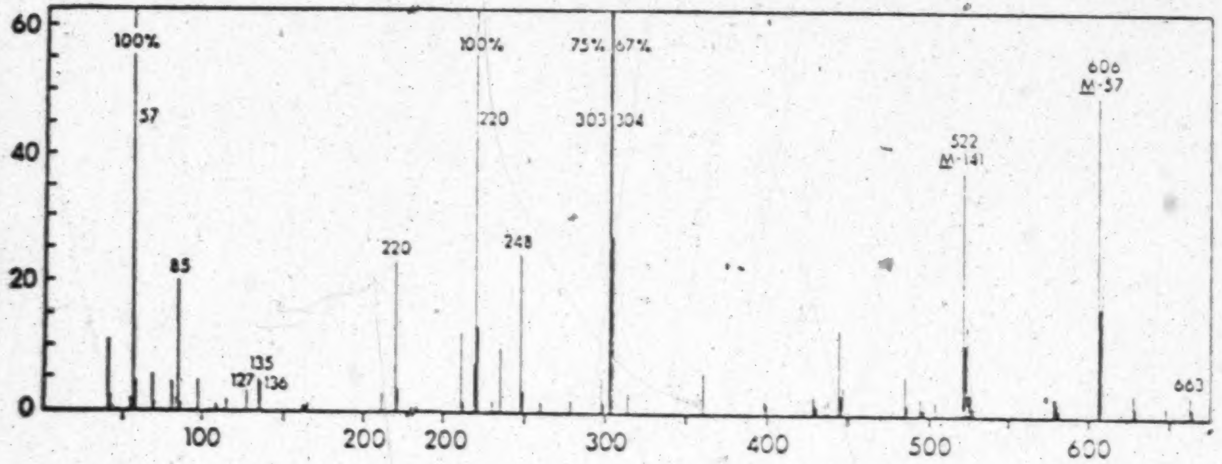


Fig. 13. 6-N-Pivalamido-9-(3-chloro-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)purine (141).

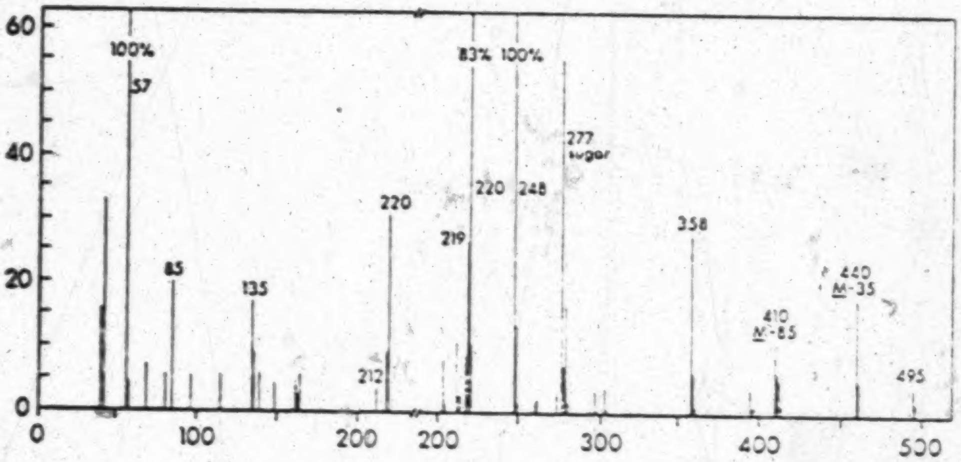
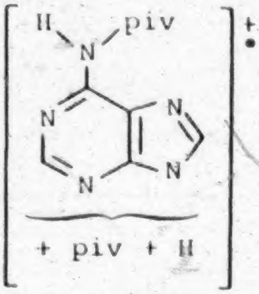


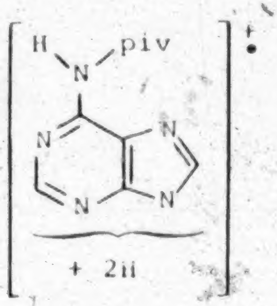
Fig. 14. 6-N-Pivalamido-9-(3-chloro-3-deoxy-2-O-acetyl-5-O-pivalyl-β-D-xylofuranosyl)purine (134).

sponding to ions: h (354), a (211), and e (127) are present. There is a change of scale in the region of m/e 200 to 250 in these mass spectra, and the relative intensities of peaks which appear on both sides of the scale change are not always the same. Therefore, the spectra of these high molecular weight compounds are presented in two parts, relative to two different mass spectral base peaks.



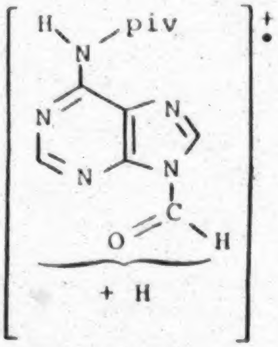
m/e 304

i



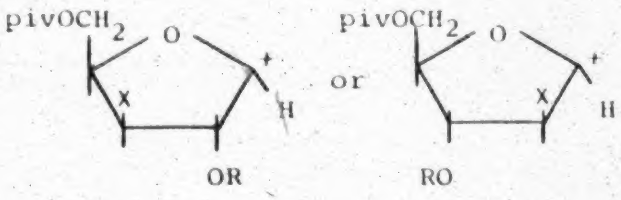
m/e 220

l



m/e 248

o



m

The peaks at m/e 127 and 211 were the first of the enolester peaks to be associated with the possibility of such a structure. While the import of much of the rest of the spectra was unclear, it was noticed that these two peaks were present in each of the, at the time, "unknown" compounds (141, 150, 151, 155, and 182), but not in the acetyl compound (134). This led to the realization that m/e 127 would correspond to formal substitution of a pivalyl (mass 85) for a proton of an acetyl fragment (mass 43, $\overset{+}{O}\equiv C\text{-}CH_3$), and that 211 was consistent with another such substitution. Accurate mass determinations of 155 gave for m/e 127: measured; 127.0762, calculated for $C_7H_{11}O_2$; 127.0759, and for 211: measured; 211.1341, calculated for $C_{12}H_{19}O_3$; 211.1334. These measurements support formulation of m/e 127 and 211 as ions e and a, respectively. Although the iodo derivatives (150 and 151) obviously have peaks at m/e 127 due to iodine, a double peak occurs at m/e 127 in these spectra, indicative of the presence of two ions at this nominal mass.

While comparison of the spectra of 134 and 141 shows some of the basic effects of the enolester group, examination of the mass spectra of the iodo-enolester compounds (150 and 151) and some of their derivatives illustrates some more subtle effects. The mass spectra of the iodo-enolesters, 150 and 151, the deoxy-enolesters,

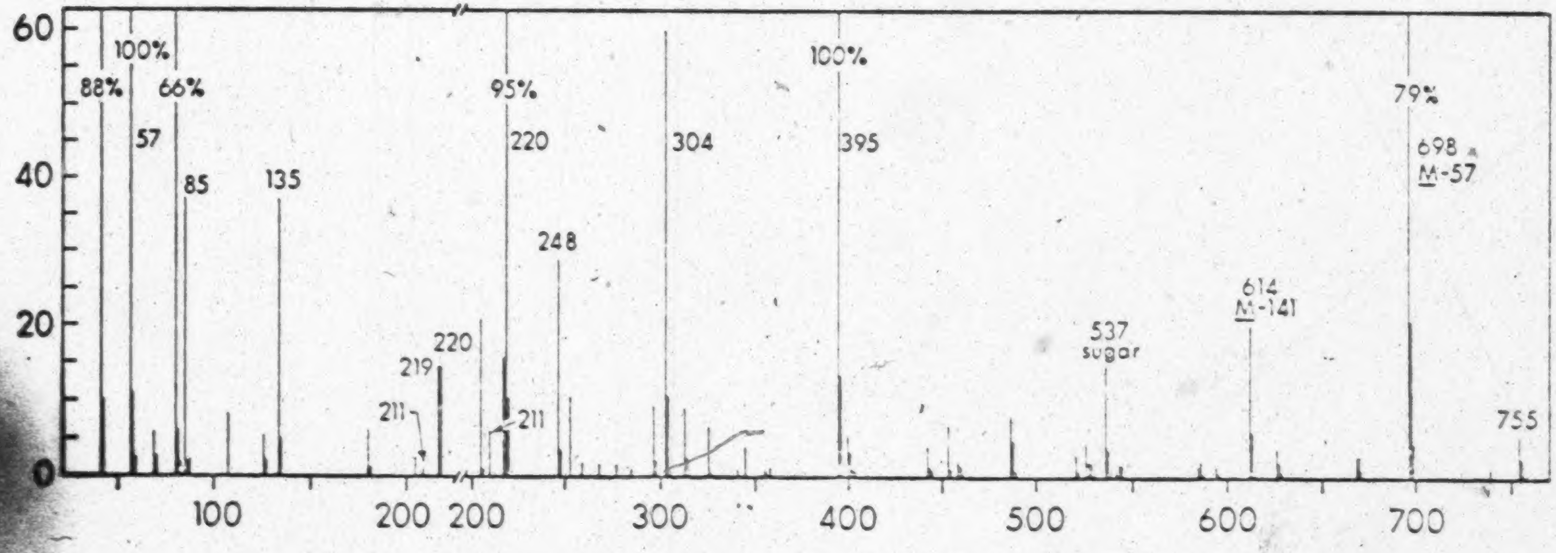


Fig. 15. 6-N-Pivalamido-9-(3-iodo-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)purine (150).

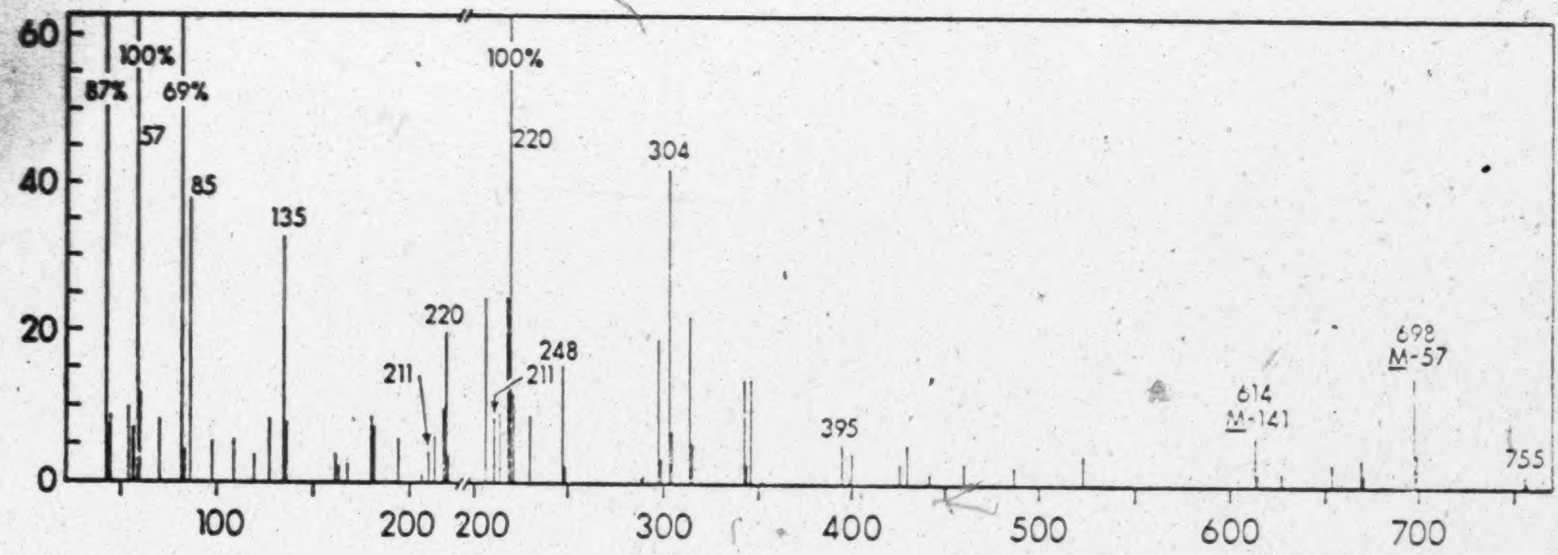


Fig. 16. 6-N-Pivalamido-9-(2-iodo-2-deoxy-5-O-pivalyl-3-O-[4,4-dimethyl-3-pivaloxy-pent-2-enoyl]-β-D-arabinofuranosyl)purine (151).

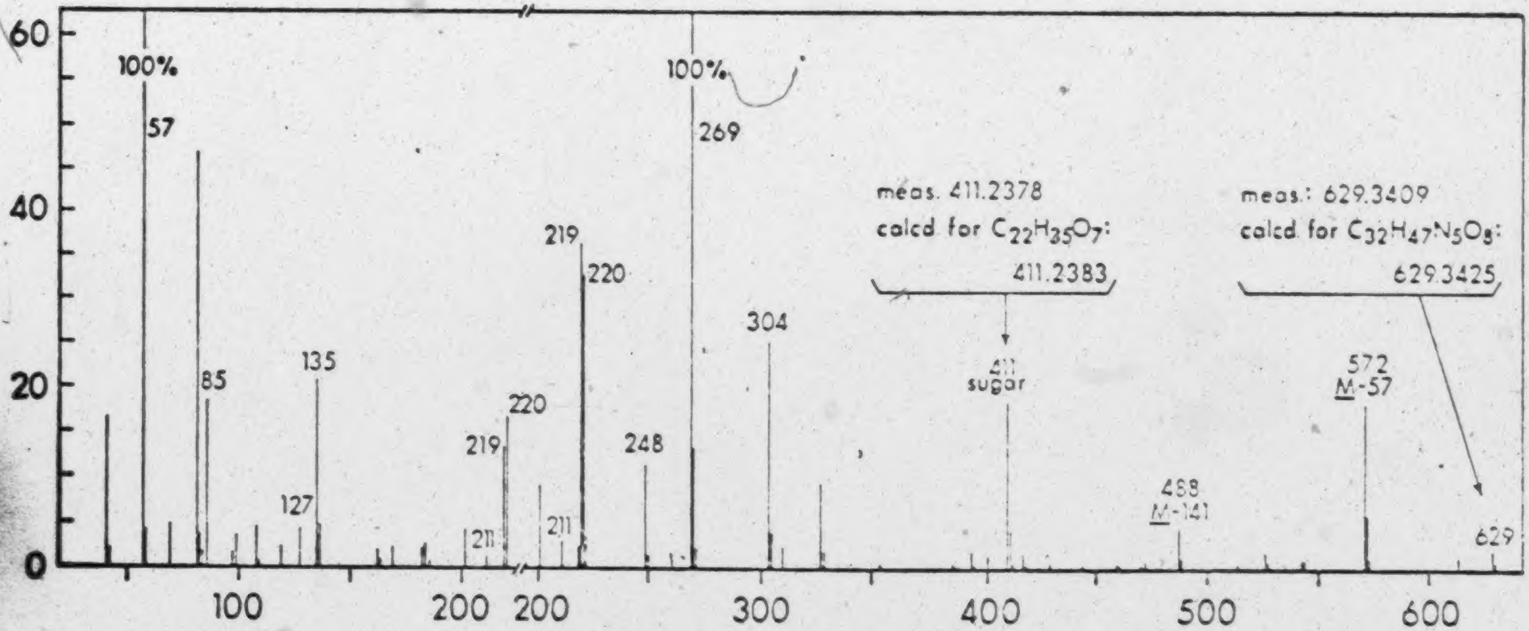


Fig. 17. 6-*N*-Pivalamido-9-(3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-*D*-*erythro*-pentofuranosyl)purine (155).

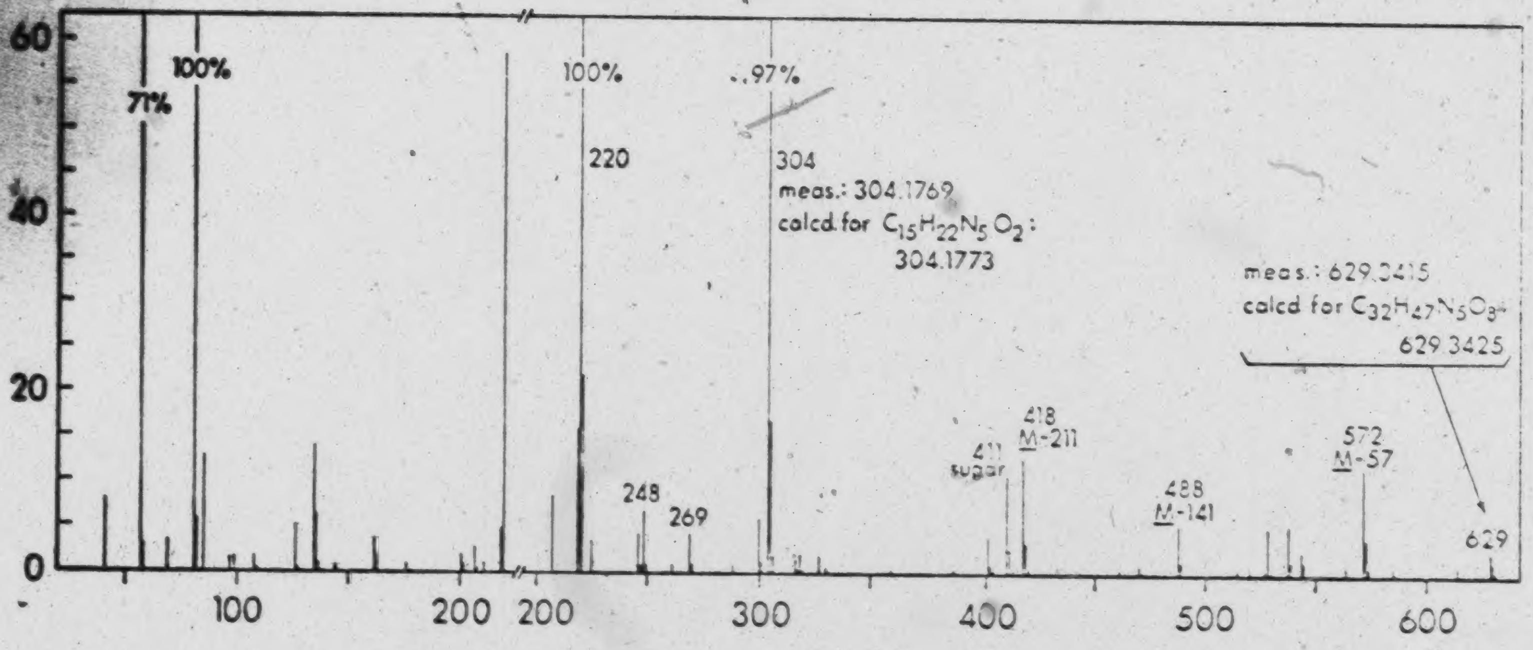


Fig. 18. 6-N-Pivalamido-9-(2-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxy-pent-2-enoyl]-β-D-*erythro*-pentofuranosyl)purine (182).

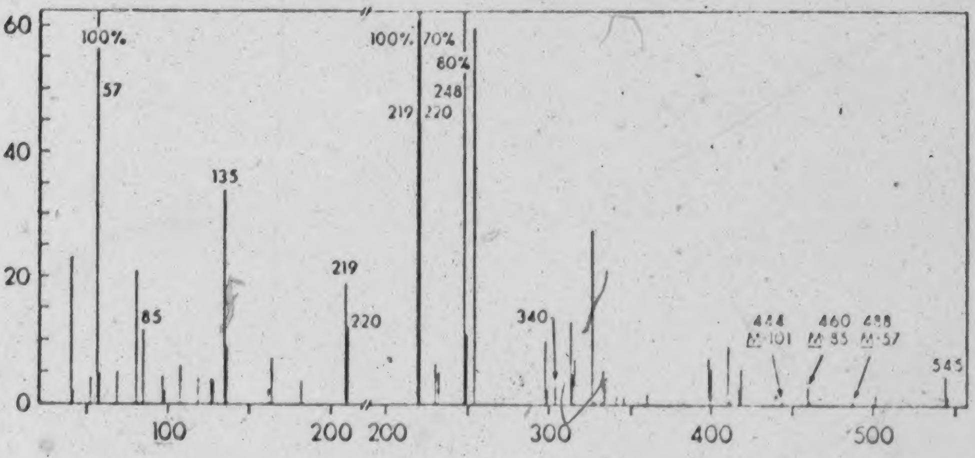


Fig. 19. 6-N-Pivalamido-9-(3-iodo-3-deoxy-5-O-pivalyl-β-D-xylofuranosyl)purine (161).

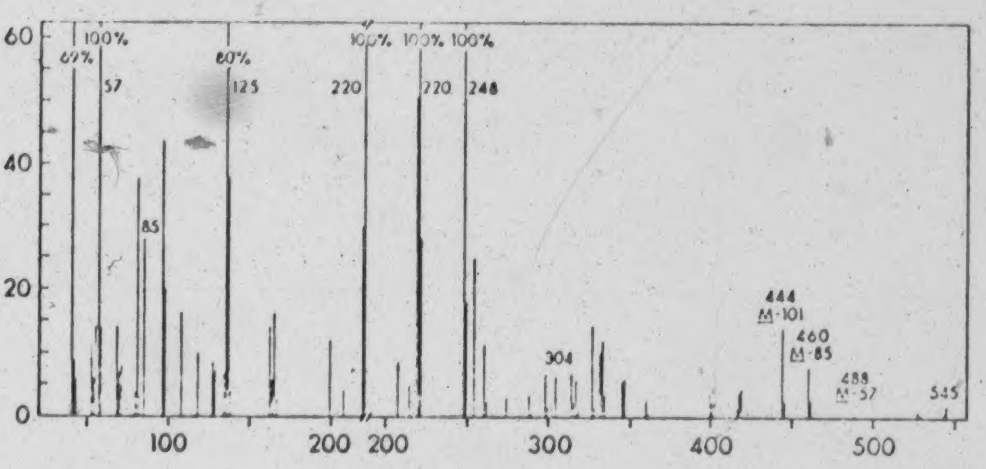
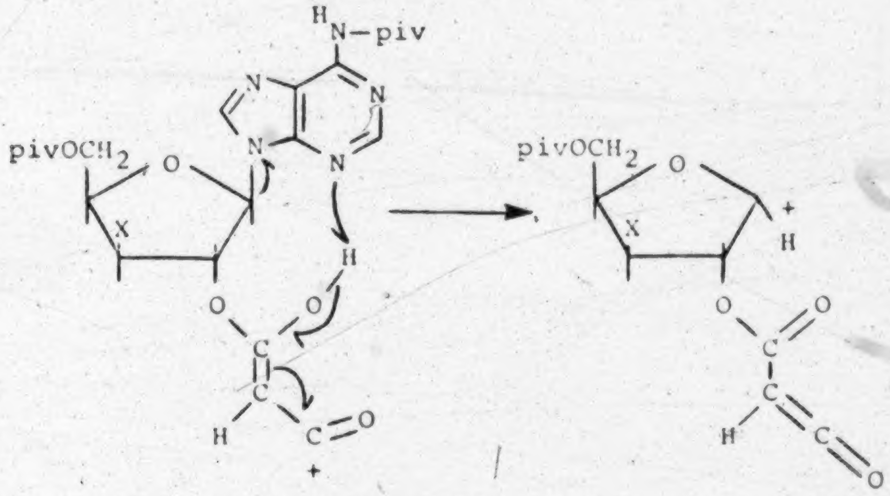


Fig. 20. 6-N-Pivalamido-9-(2-iodo-2-deoxy-5-O-pivalyl-β-D-arabinofuranosyl)purine (164).

154 and 182, and the iodo-hydroxy compounds, 161 and 164, are shown in Figures 15 to 20. Only the enolester derivatives show significant peaks for ions c, h, and j. Ion j was also very small in the spectrum of 134, which suggests that the formation of ion j occurs by transfer of the enolester O-pivalyl group to the base in preference to transfer of the 5'-O-pivalyl. Unlike the chloro compounds 134 and 141, whose spectra were determined on mixtures of isomers, the spectra shown in Figures 15 to 20 are of isomerically pure materials and a marked difference between the 2'- and 3'-isomers can now be seen. Thus for 150 and 154, ion k (395 and 269, respectively, ion h-218) is the largest peak and ion j (304) is at most 60% of k. This situation is reversed with the 2'-isomers 151 and 182, where either m/e 304 (j) or 220 (l) (which can be derived from j) are the largest peaks, and ion k is quite small. The origin of ions j, k, and l can be found in metastable peaks. The iodo compounds show peaks corresponding to: 614 (h) to 395 (k), at 236; 755 (M) and 698 (c) to 304 (j), at 122.5 and 132.5. The deoxy derivatives show metastable peaks corresponding to 572 (c) to 304 (j), at 162; 304 (j) to 220 (l), at 159; and 488 (h) to 269 (k), at 148. The fact that ion k is formed from h and that it is more important in the 3'-iodo or 3'-deoxy isomers suggests that the proton transferred to the

base may be from the remainder of the enolester fragment. This transfer should be easier with the fragment at the 2'-position.



c   i

Scheme XXXVIII

The formation of ion i from either the parent ion or ion b supports the preferential involvement of the enolester pivalyl group. Apparently this transfer is more favorable with the 3'-O-enolester (the 2'-iodo or 2'-deoxy compound) than with the 2'-O-enolester. The fragmentation of this enolester function is therefore not only characteristic, but is also indicative of its position of attachment to the sugar.

In the mass spectrum of the tubercidin 3'-iodo-2'-O-enolester derivative (171, Figure 21) all fragments which contain the heterocyclic base appear one mass unit lower than their adenosine counterparts because of the one unit mass difference between adenine and 4-amino-pyrrolo[2,3-d]pyrimidine. Thus, ions c, and h are at m/e 697, and 613, respectively. In this case the largest peak is the sugar fragment (537, ion m) and loss of 84 from the sugar fragment is similarly large, while ions j and k are now quite small. Although the relative intensities of many of the peaks are different from those in the spectrum of 150, the spectra are otherwise closely analogous.

The nmr spectra (in DMSO-d_6, D_2O) of the adenosine and tubercidin deoxy derivatives 5, 167, 18, 61, 174, and 175 are shown in Figures 22 to 27. In each case the 5' and 5" protons for a β nucleoside (where the 5'-carbon is cis to the base) give rise to a complex multiplet, while this signal appears as a clean doublet (after D_2O exchange) for the α-nucleosides (where the 5'-carbon is trans to the base). This is presumably the result of steric, 5'-O to base hydrogen bonding, and/or base anisotropy 5', 5" chemical shift difference effects on the 5'-position, which are eliminated when the base and hydroxymethyl groups

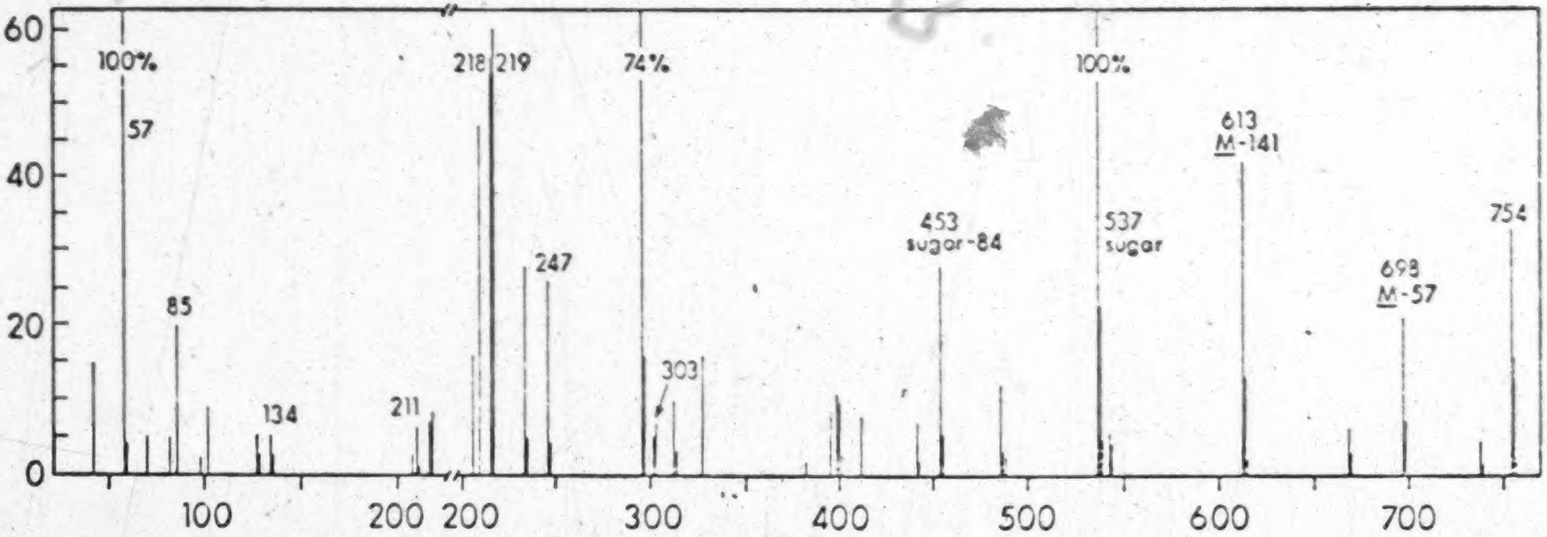


Fig. 21. 4-N-Pivalamido-7-(3-iodo-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)pyrrolo [2,3-d]pyrimidine (171).

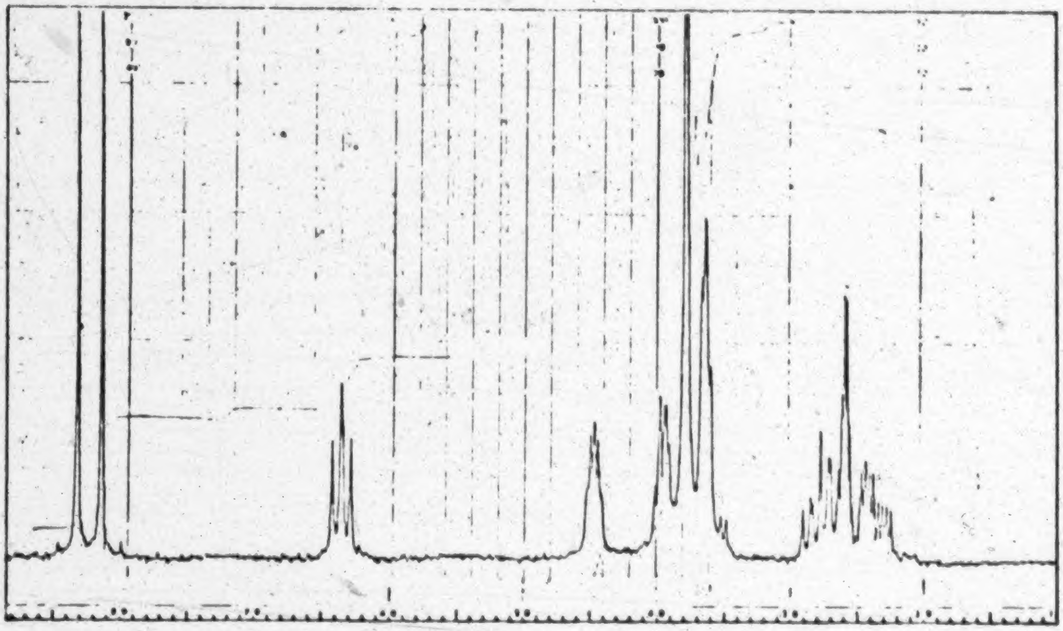


Fig. 22. 2'-Deoxyadenosine (5) (DMSO-d_6, D_2O).

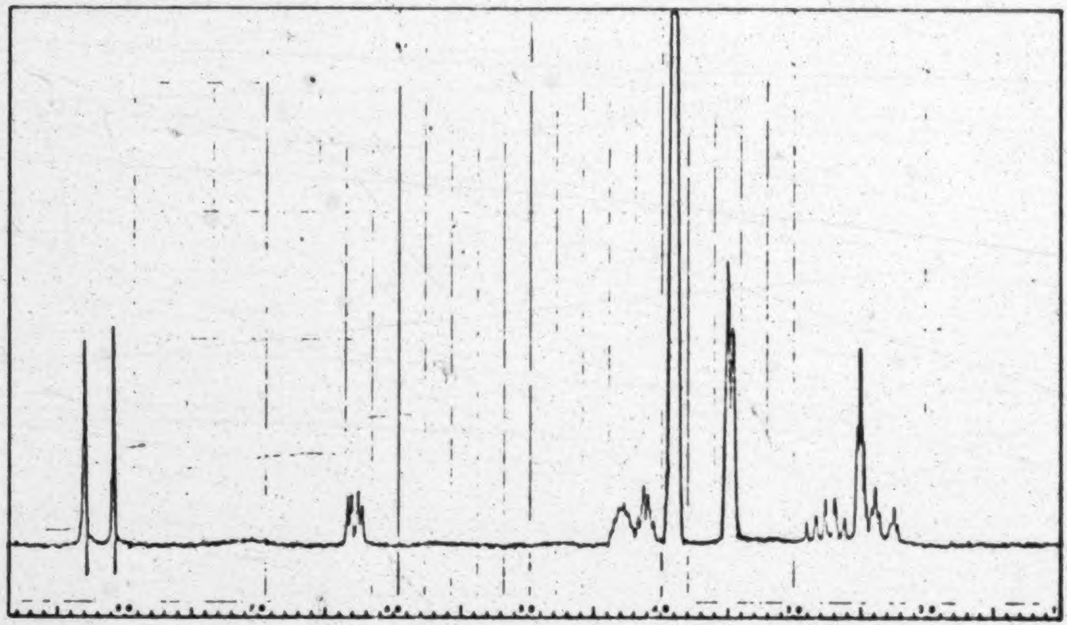


Fig. 23. 6-Amino-9-(2-deoxy-α-D-erythro-pentofuranosyl)-purine (167) (DMSO-d_6, D_2O).

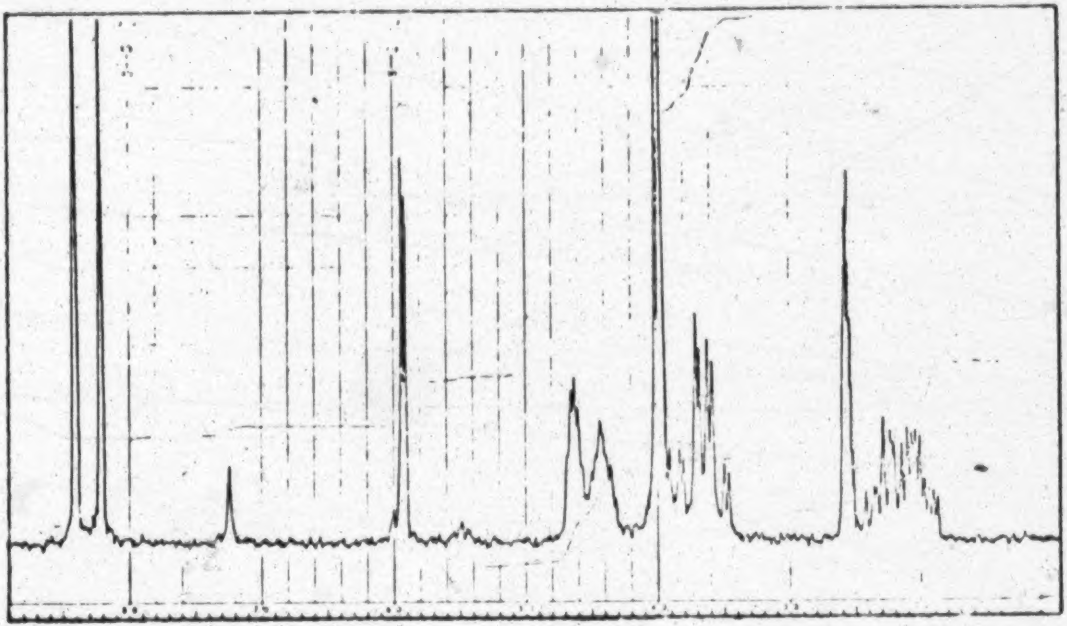


Fig. 24. 3'-Deoxyadenosine ($\underline{18}$) (DMSO-$\underline{d}_6$, D_2O).

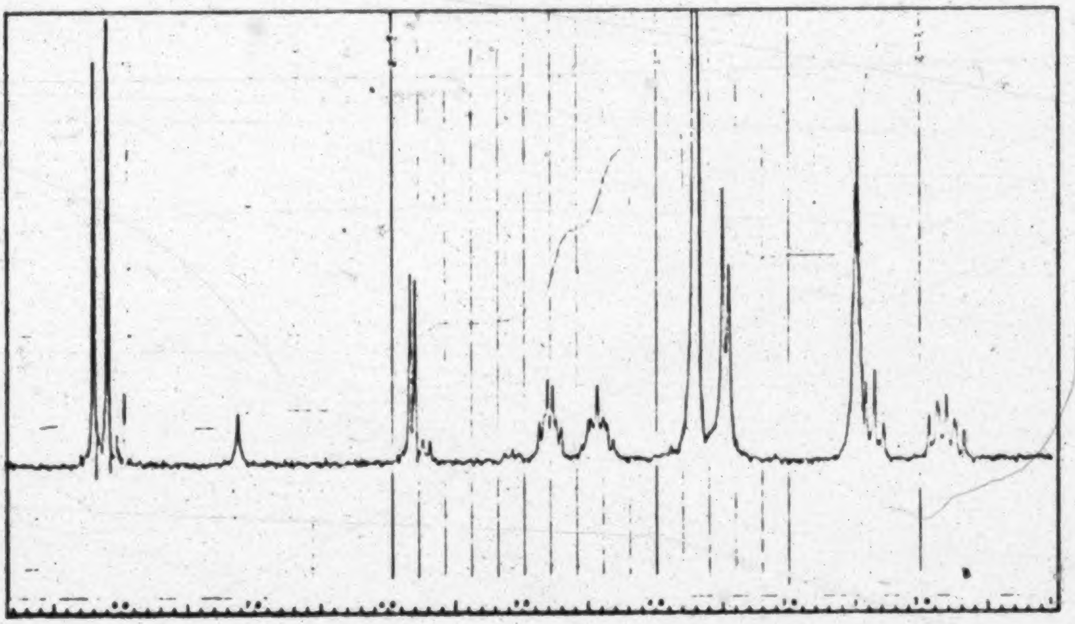


Fig. 25. 6-Amino-9-(3-deoxy-α-$\underline{L}$-$\underline{threo}$-pentofuranosyl)purine ($\underline{61}$) (DMSO-$\underline{d}_6$, D_2O).

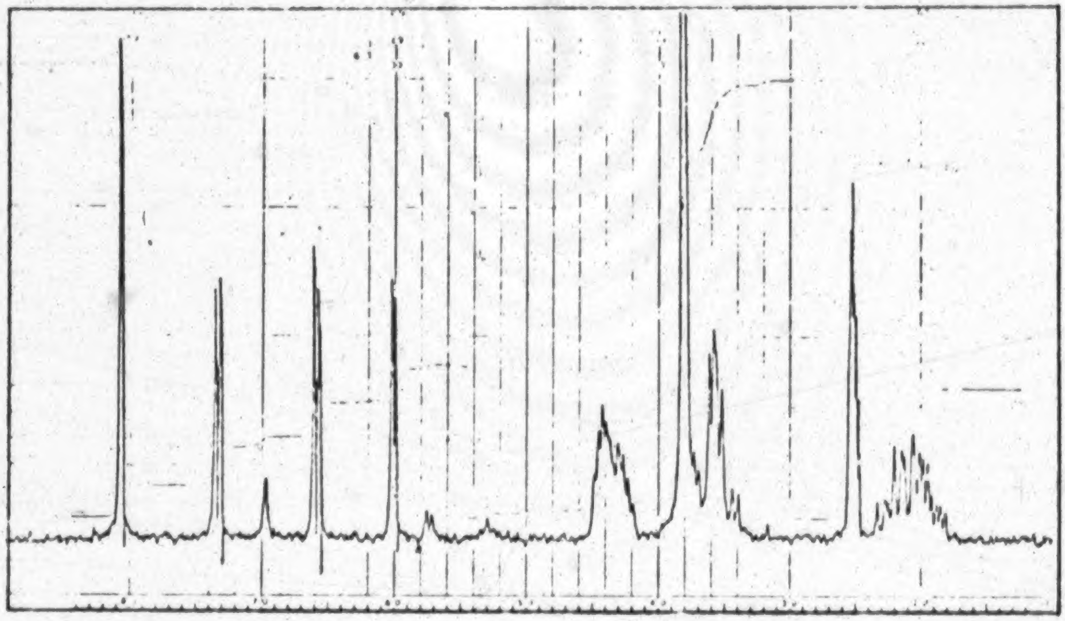


Fig. 26. 3'-Deoxytubercidin (174) (DMSO-d_6, D_2O).

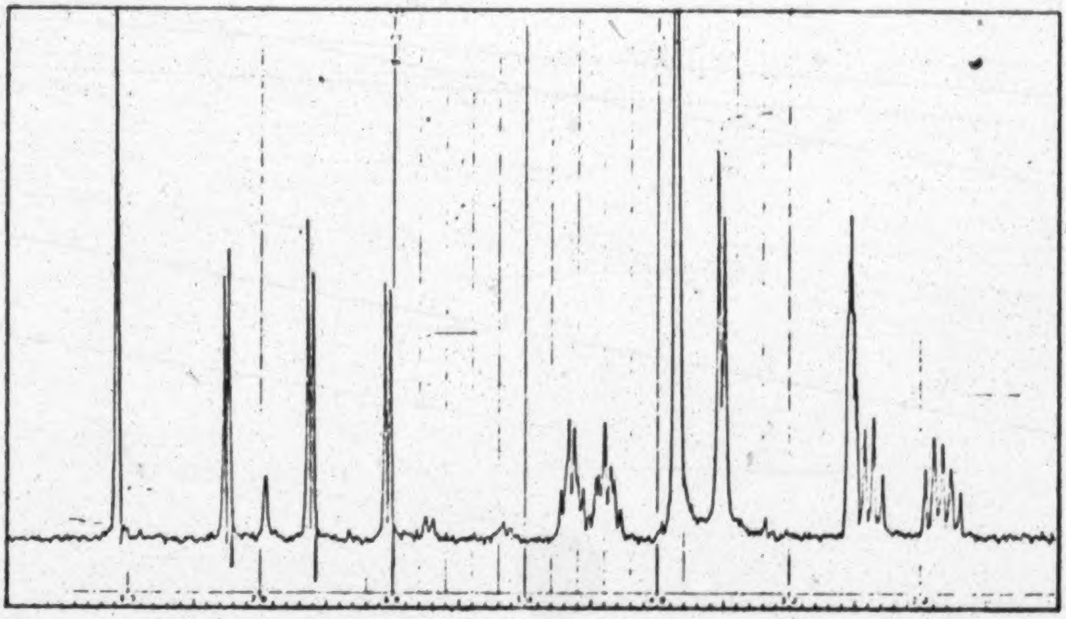


Fig. 27. 4-Amino-7-(3-deoxy-α-L-threo-pentofuranosyl)pyrrolo-[2,3-d]pyrimidine (175) (DMSO-d_6, D_2O).

are trans. The spectra (Figures 28 and 29) of the adenosine and tubercidin 2',3'-dideoxy racemates obtained from hydrogenation of the corresponding furyl compounds (157 and 173) also show the complex pattern for the 5',5"-protons. This indicated the exclusive cis stereochemistry which was confirmed by N^6,5'-cyclonucleoside formation. In addition, the nmr spectrum of 2',3'-dideoxy adenosine obtained by hydrogenation of 2',3'-unsaturated adenosine (46)[81] is identical with that of the racemate. It is also interesting that with the 3'-deoxy compounds the 3' and 3" protons are well separated in the α-L-threo (61 and 175), but only slightly in the β-D-erythro (18 and 174) nucleosides. Nagpal and Horwitz had earlier noted only that differentiation between 18 and 61 via nmr spectroscopy was not possible by examination of the resonance due to the 4' proton.[94]

A close similarity in the splitting pattern of the deoxy protons is seen with 2'- and 3'-deoxyadenosine (Figure 30). In fact, the respective couplings are almost identical. Apparently with both the base and the 5'-carbon trans to the remaining hydroxyl, the 3'/2', exo/endo ring puckering of each is exactly reversed with respect to the other. This does not hold for the 2'-deoxy α-D (167, Figure 23) and 3'-deoxy-α-L (61 and 175, Figures 25 and 27) compounds which exhibit quite different

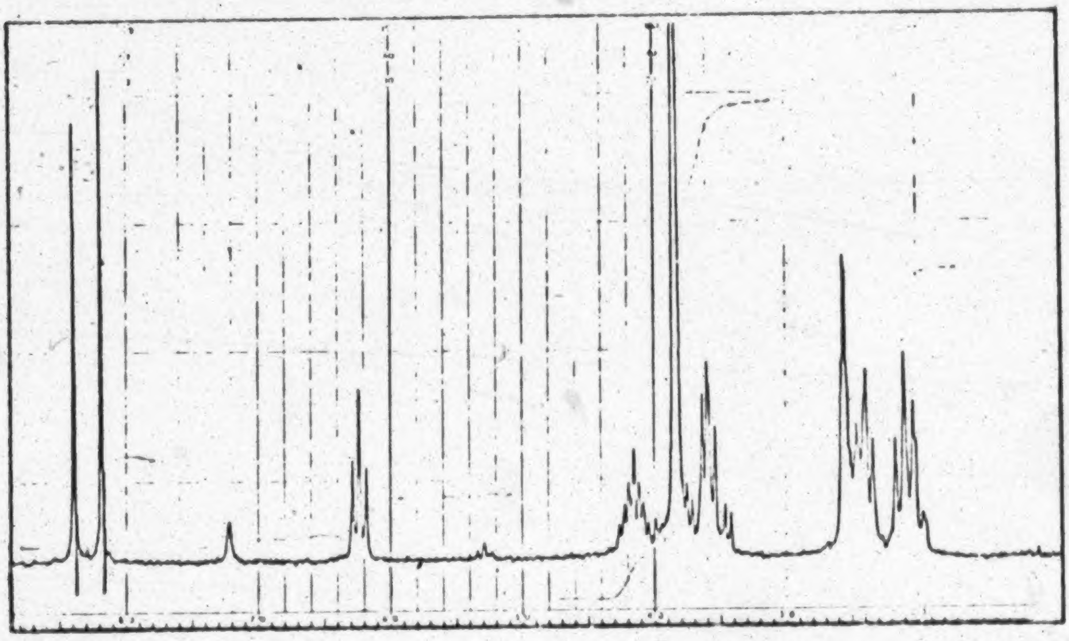


Fig. 28. Racemic 2',3'-Dideoxyadenosine (20 and 169) (DMSO-$\underline{d}_6$, D_2O).

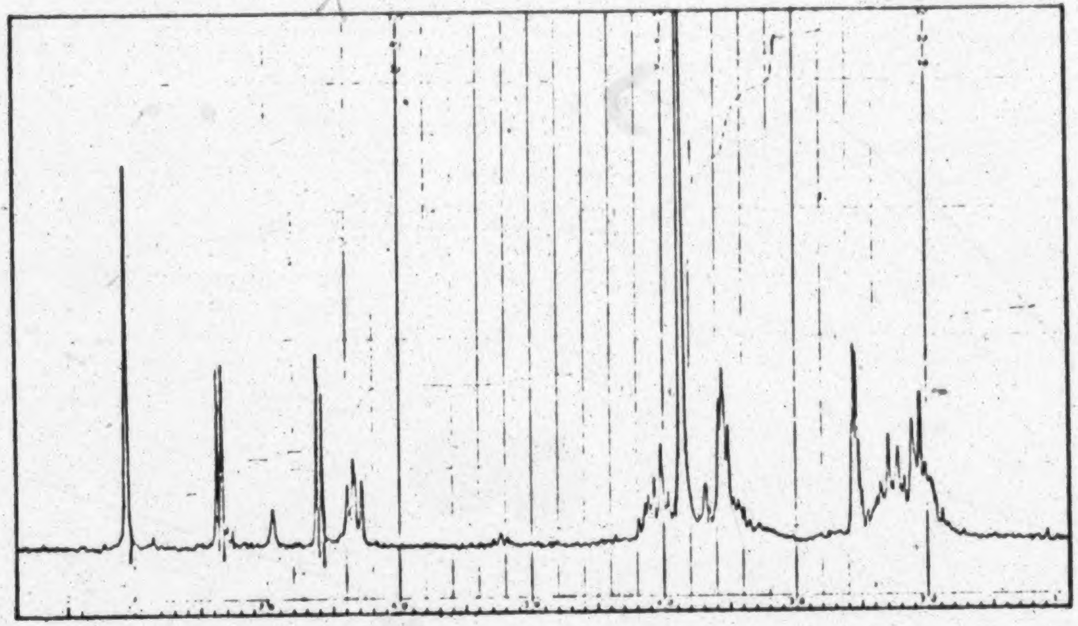
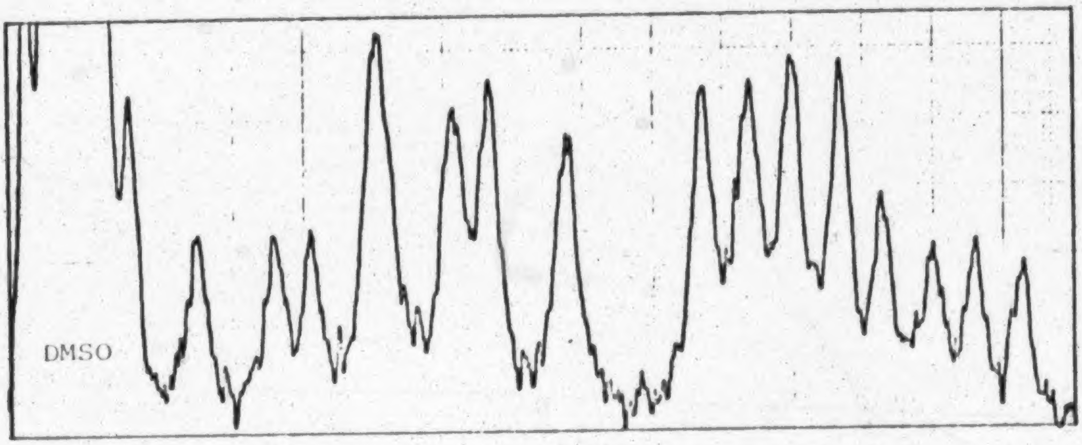
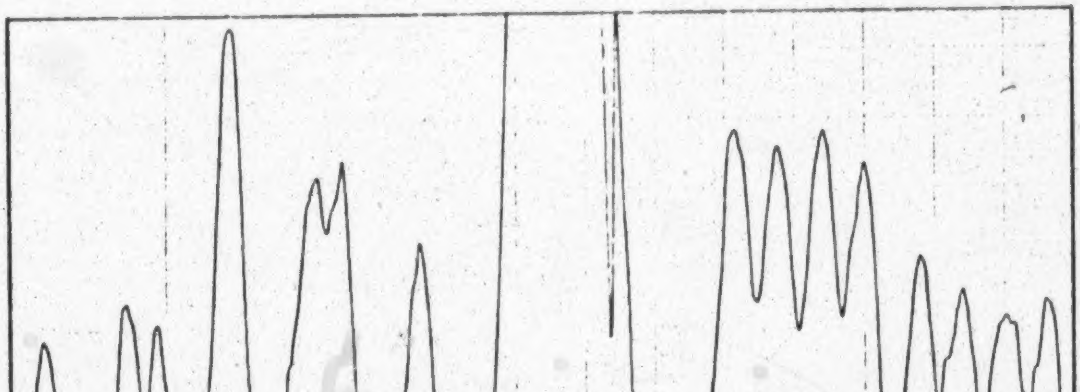


Fig. 29. Racemic 2',3'-Dideoxytubercidin (178 and 179) (DMSO-$\underline{d}_6$, D_2O).



3'-deoxy



2'-deoxy

Fig. 30. Deoxy Protons of 2'-Deoxyadenosine (5) and 3'-Deoxyadenosine (18) (DMSO-$\underline{d}_6$).

patterns. In these examples the base and 5'-carbon are *cis* and *trans* or *trans* and *cis*, respectively, to the hydroxyl. As would be expected, the adenosine and tubercidin epimers show very similar patterns for each β-*D* (**18** and **174**, Figures 24 and 26) and α-*L* pair (**61** and **175**, Figures 25 and 27).

The nmr spectra of the 3',4'-unsaturated adenosine (**156**) and tubercidin (**173**) compounds (Figures 31 and 32), like their blocked counterparts, are analogous in the sugar region, although in the tubercidin case the 2' and 3' protons are at least separated, if still unresolved. Conversely, 1',2'-unsaturated adenosine (**159**, Figure 33) gives very well resolved peaks showing $J_{2',3'}$ = 2.75 Hz, $J_{3',4'}$ = 3.0 Hz, $J_{4',5'}$ = 5.0 Hz and hydroxyl couplings of 6.0 Hz. Although many of these couplings can be determined directly, decoupling was used to confirm the couplings and assignments. The 2',3'-unsaturated compound (**46**, Figure 34) is also noteworthy for its sharply resolved, although complex signals. The complexity is the result of each of the 1',2',3', and 4' protons being coupled to the other.

McClosky has noted that mass spectra of free nucleosides have a peak at *M*-30 for loss of the 5'-function as formaldehyde. Transfer of the 5'-hydroxyl proton to the base occurs and this *M*-30 peak was shown to be significant only when the 5'-hydroxyl is *cis* to

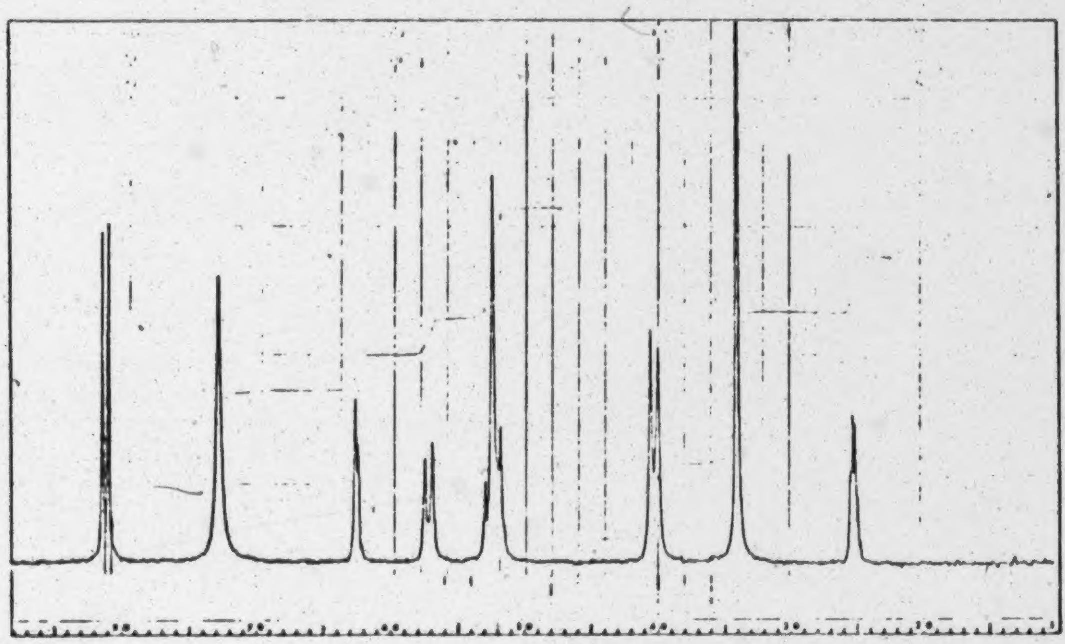


Fig. 31. 6-Amino-9-(3-deoxy-β-D-glycero-pent-3-enofuranosyl)-purine (156). (DMSO-d_6).

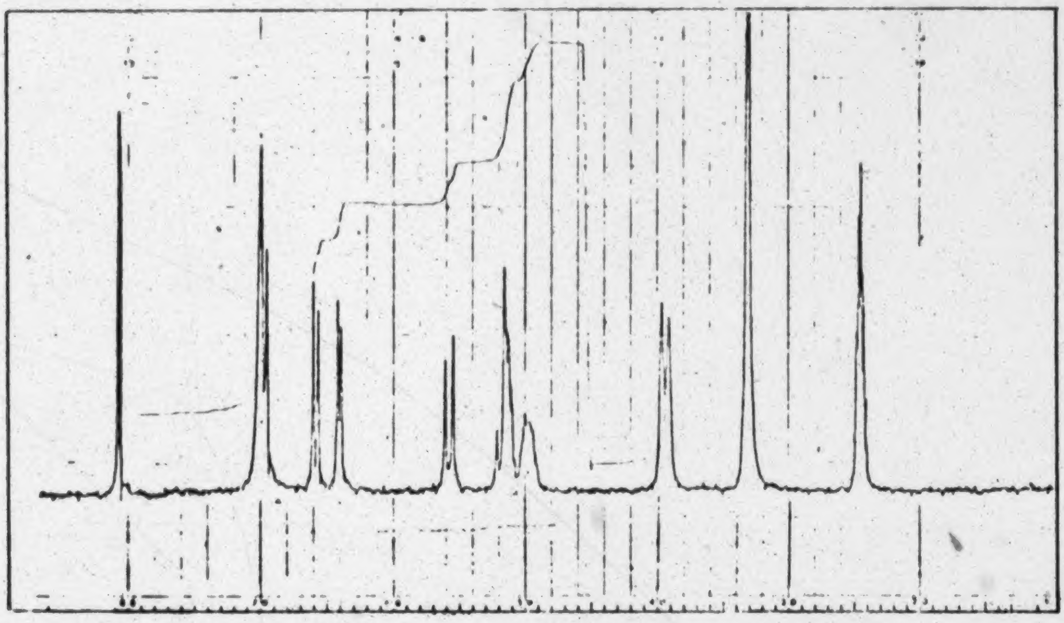


Fig. 32. 4-Amino-7-(3-deoxy-β-D-glycero-pent-3-enofuranosyl)-pyrrolo[2,3-d]pyrimidine. (173). (DMSO-d_6).

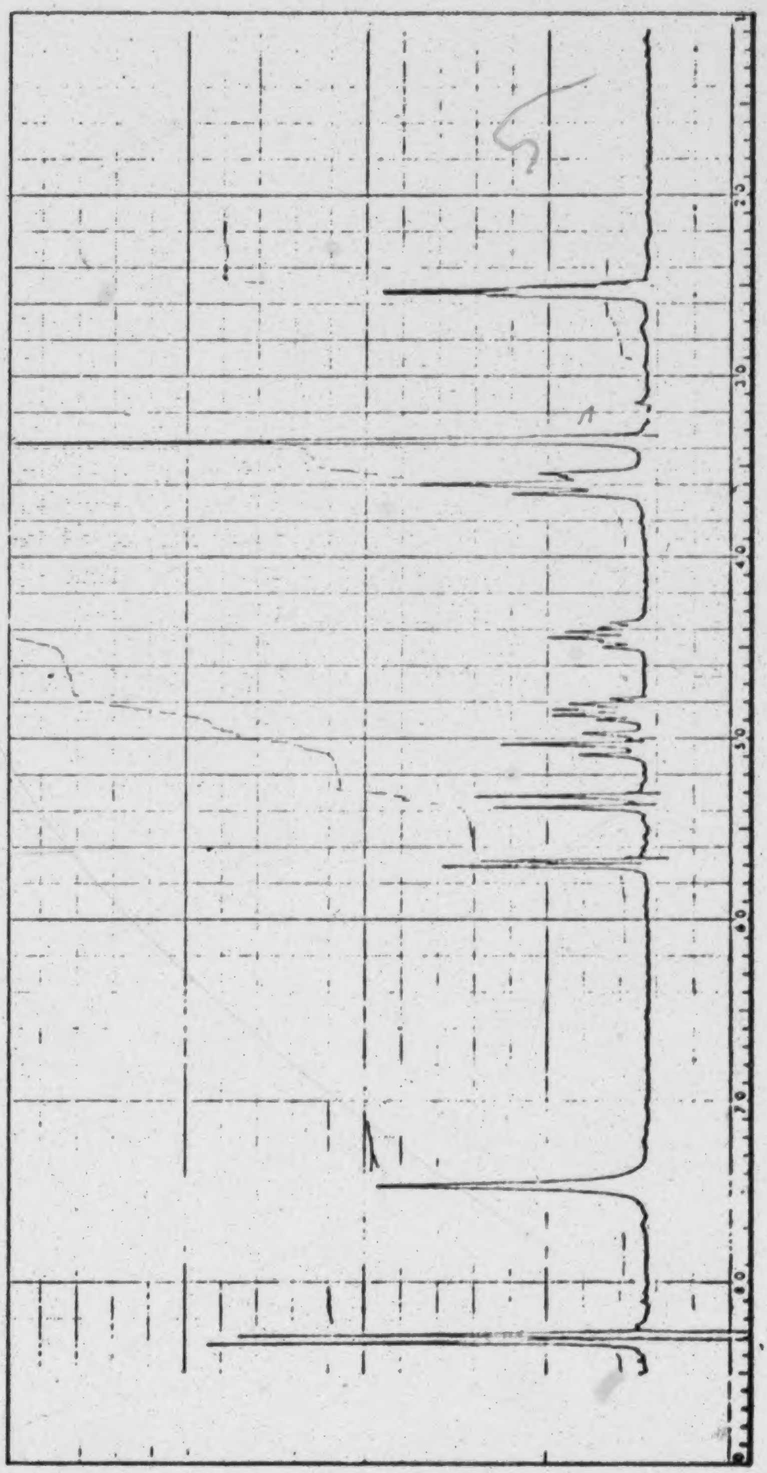


Fig. 33. 6-Amino-9-(2-deoxy-D-erythro-pent-1-enofuranosyl)purine (159). (DMSO-d-$_6$).

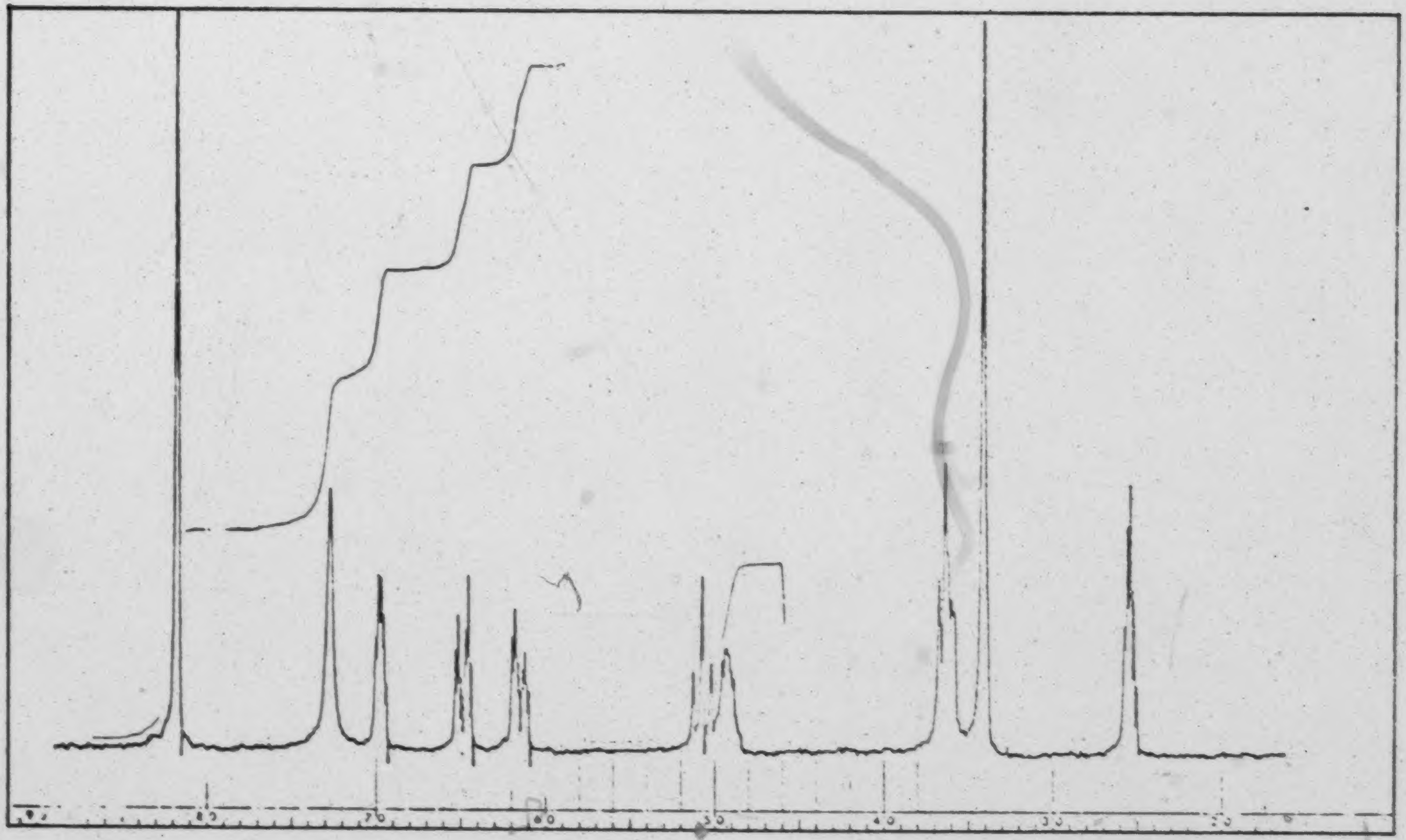


Fig. 34. 6-Amino-9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)purine (46). (DMSO-$\underline{d}_6$).

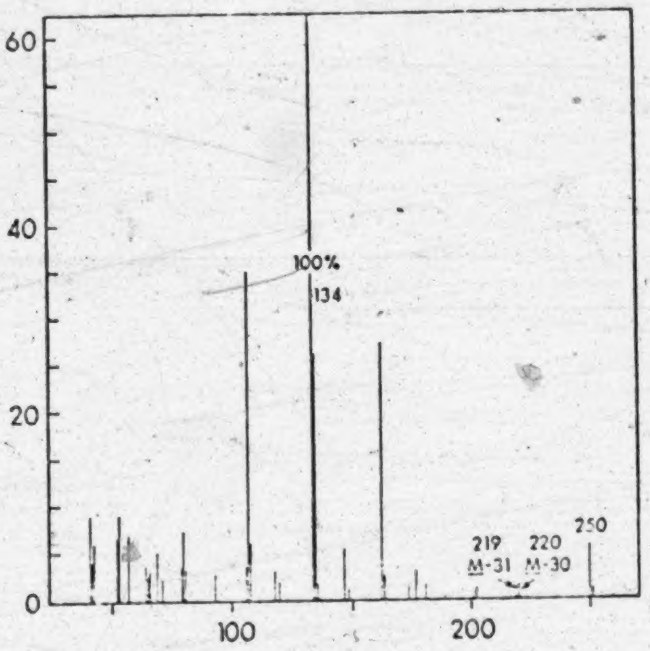


Fig. 35. 3'-Deoxytubercidin (174).

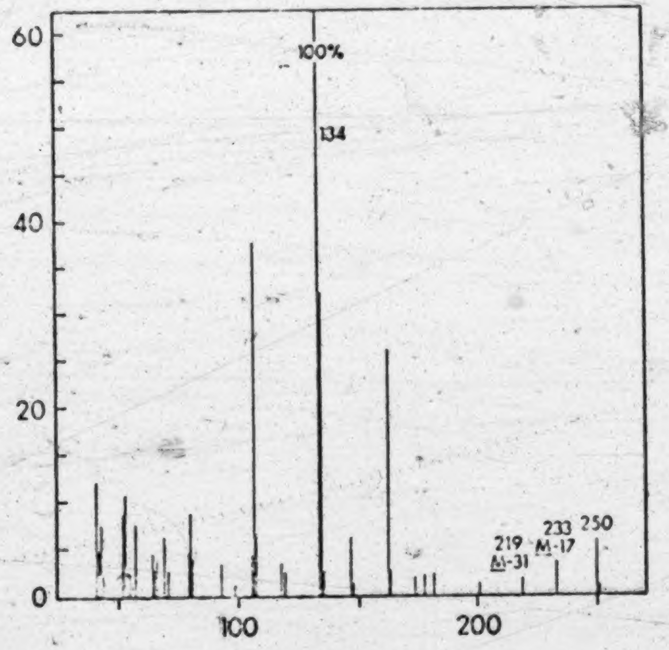


Fig. 36. 4-Amino-7-(3-deoxy-α-L-threo-pentofuranosyl)-pyrrolo[2,3-d]-pyrimidine (175).

the base.[164] In this regard, the spectra of 2'-deoxy-β-*D* adenosine and its α-*D* anomer were discussed and the much smaller *M*-30 peak of the α anomer noted. Similarly, Nagpal and Horwitz showed that the 4' epimer of 3'-deoxyadenosine lacked this *M*-30 peak and have published the mass spectrum of *61*.[94] The spectra obtained in the present case were identical with those reported by McCloskey and by Horwitz and are therefore not reproduced here. The spectra of the 4' epimers of 3'-deoxytubercidin are shown (Figures 35 and 36) and the *M*-18 peak in place of the *M*-30 peak in the spectra of the α-*L* compound (*175*, Figure 36) is analogous to the spectrum of the corresponding adenosine derivative (*61*). The racemic adenosine 2',3'-dideoxy compound (Figure 37) has a mass spectrum identical with the spectrum of the known β-*D*-dideoxyadenosine reported by McCloskey[164] as well as material obtained in the present case from hydrogenation of 2',3'-unsaturated adenosine.[81] The spectrum of the racemic 2',3'-dideoxy tubercidin compound (Figure 38) was completely analogous.

The parent peak for the blocked 1',2'-unsaturated adenosine derivative (*166*) was very small, and for the free nucleoside was not observable. Loss of H_2O to give the corresponding furyl derivative predominates with these compounds. Thus, the spectra of *166* and the

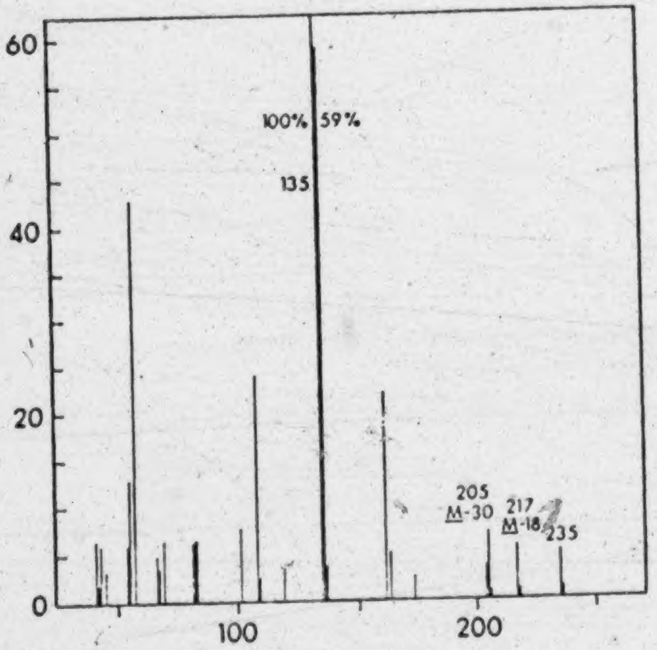


Fig. 37. Racemic 2',3'-Dideoxyadenosine (20 and 169).

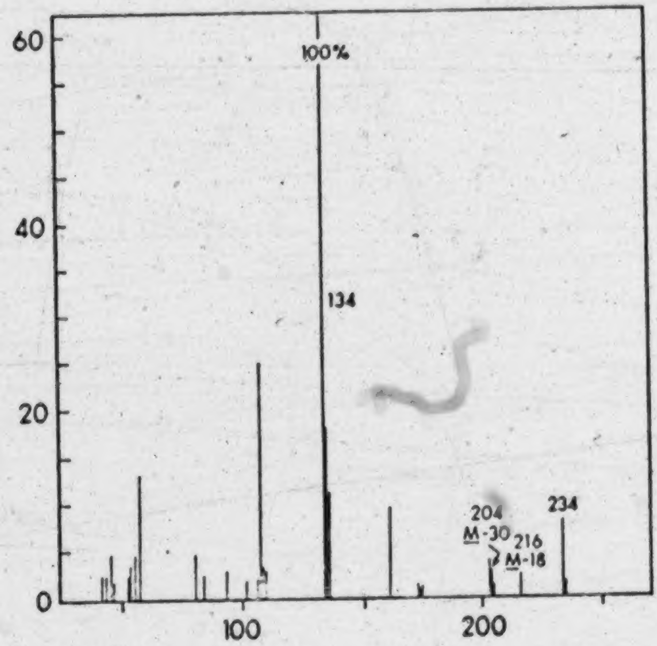


Fig. 38. Racemic 2',3'-Dideoxytubercidin (178 and 179).

furyl derivative (153) (Figures 39 and 40) are nearly identical, although the former shows peaks for base + 30, base + H, and base + 2H which are not present in the spectrum of 153. However, the free nucleoside gave only the spectrum of the furyl derivative (157). The mass spectrum of the parent structure in this case could only be obtained by per-trimethylsilylation and is shown in Figure 41.

The blocked 3',4'-unsaturated compounds (152 and 172) also gave only the mass spectra of their furyl derivatives (153 and 176). However, in this case the mass spectrum of the free nucleoside did show the parent structure, although dehydration to the furyl compound was still a major process. Figures 42 and 43 show the mass spectra of 3',4'-unsaturated adenosine (156) and the furyl derivative (157) for comparison.

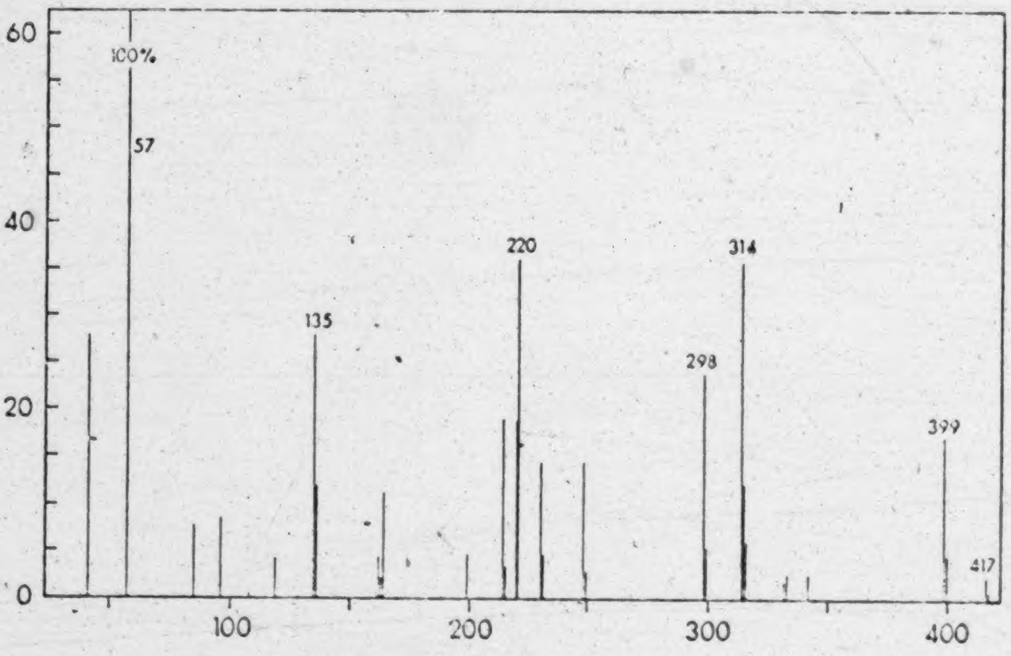


Fig. 39. 6-N-Pivalamido-9-(5-O-pivalyl-D-*erythro*-pent-1-enofuranosyl)-purine (166).

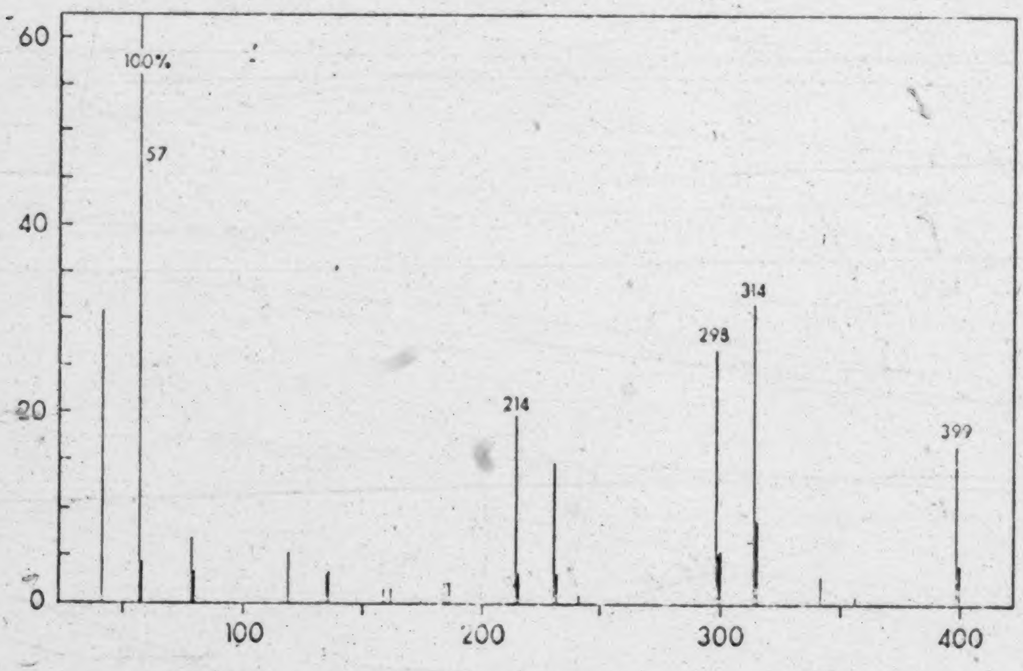


Fig. 40. 6-N-Pivalamido-9-(5-pivaloxymethyl-2-furanyl)purine (153).

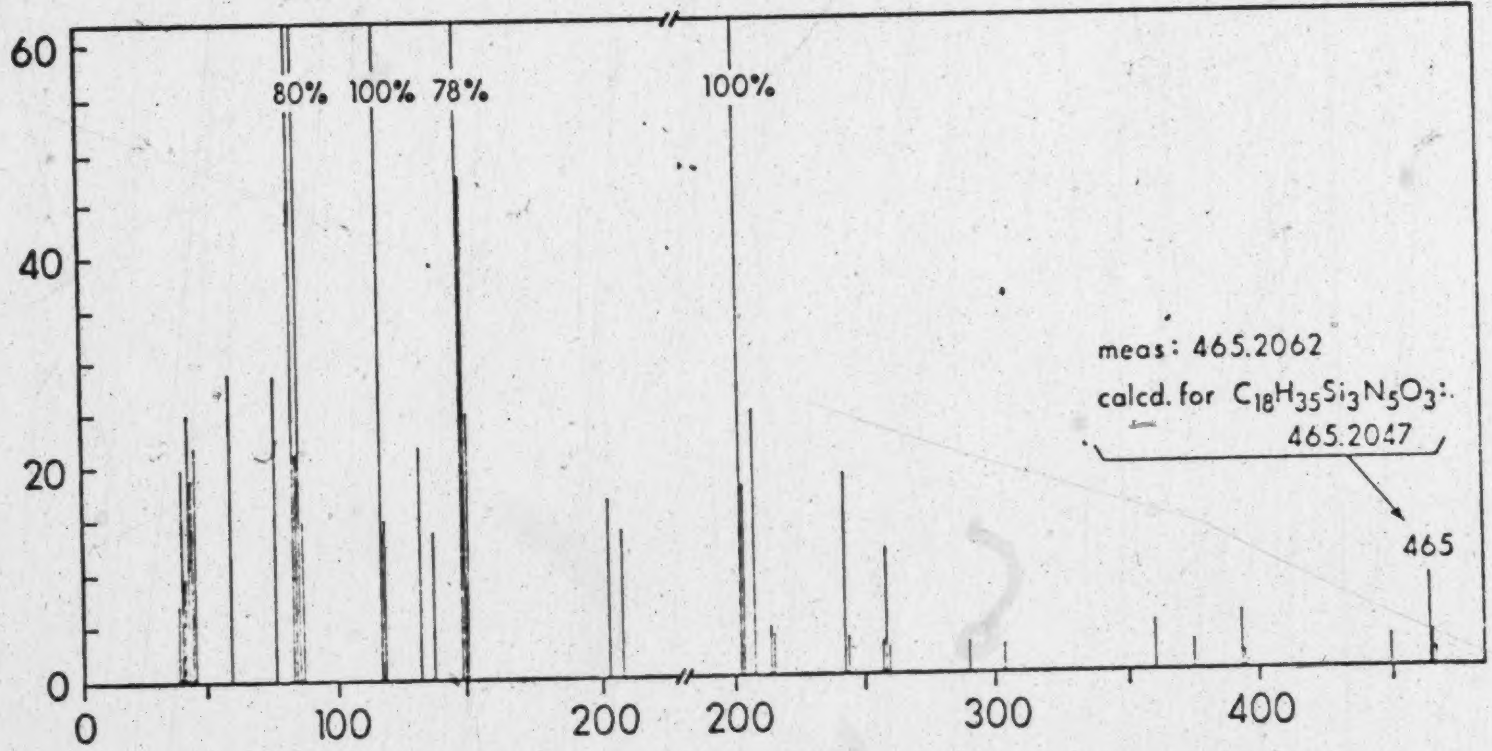


Fig. 41. 6-N-Trimethylsilylamino-9-(2-deoxy-3,5-bis-O-trimethylsilyl-D-erythro-pent-1-enofuranosyl)purine.

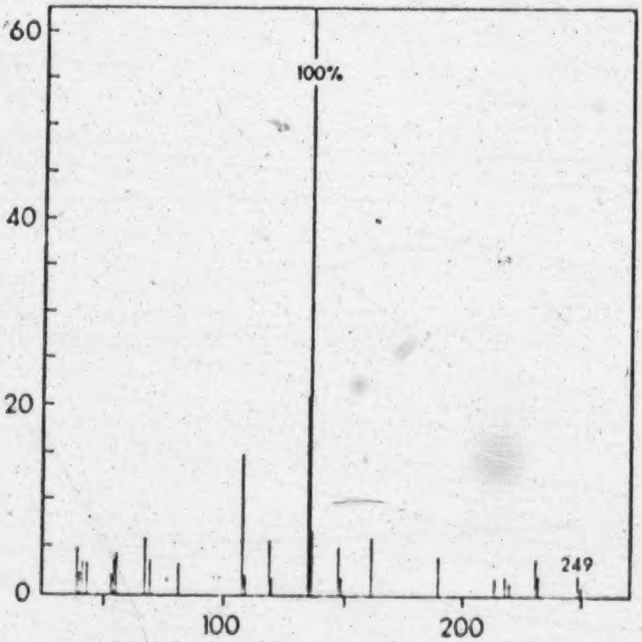


Fig. 42. 6-Amino-9-(3-deoxy-β-D-glycero-pent-3-eno-furanosyl)purine (156).

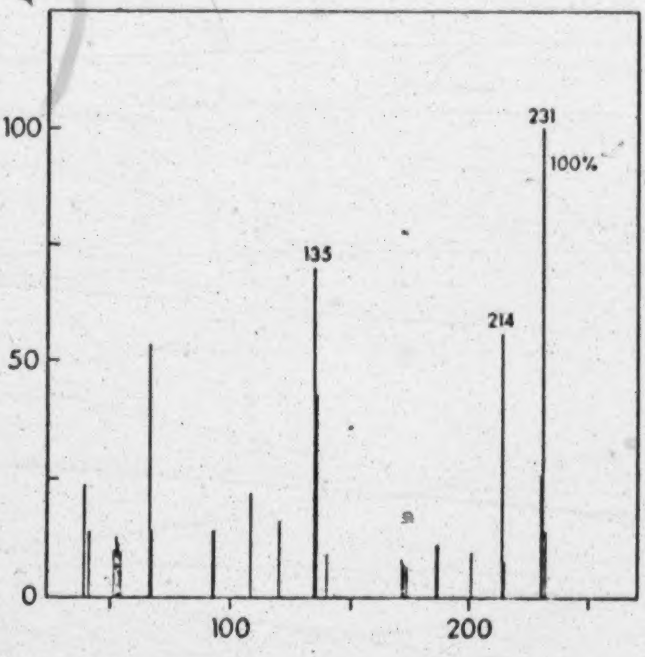


Fig. 43. 6-Amino-9-(5-hydroxymethyl-2-furanyl)purine (157).

EXPERIMENTAL

A. GENERAL PROCEDURES

Melting points were determined on a Reichert microstage apparatus and are uncorrected. Nuclear magnetic resonance spectra (nmr) were recorded on Varian A-60 and HA-100 instruments with TMS as reference. Ultraviolet (uv) spectra were recorded on Cary 14 or 15 spectrophotometers by 9:1 dilution of a methanolic stock solution with the specified solvent. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter using a 10 cm, 1 ml microcell. Mass spectra were obtained by the Mass Spectroscopy Laboratory at The University of Alberta on AEI MS-2, MS-9, or MS-12 instruments via direct probe sample introduction at 70 eV and 150 to 230°. Elemental analyses were determined by the microanalytical laboratory of this department or by Schwarzkopf Microanalytical Laboratory, Woodside, New York. Thin layer chromatography (tlc) was performed on Eastman Chromatogram sheets (silica gel No. 13181, indicator No. 6060) in the solvent systems indicated. Developed chromatograms were evaluated under uv (2537 Å) light. Evaporations were carried out using a Büchler rotating evaporator with a Dry Ice cooled Dewar condensor under aspirator or oil pump vacuum, at 40° or less. Hydrogenations were effected using a Parr shaking apparatus at room temperature, under the specified hydrogen pressure with Matheson, Coleman and Bell 5 or 10% palladium on carbon as catalyst.

Silica gel column chromatography was performed on Mallinckrodt SilicAR CC-7 or J. T. Baker No. 3405 silica gel. Unless "Baker" is specified "silica gel" refers to the Mallinckrodt CC-7 adsorbent. Carbon chromatography was effected on Barnebey-Cheney AU-4 carbon which was refluxed with 1 N HCl for several hours, washed with water and refluxed with 1 N NaOH. The carbon was then washed with water until the filtrate was neutral, followed by methanol, chloroform, and methylene chloride, and allowed to air dry. "Ether" refers to Mallinckrodt diethyl ether in all cases. Pyridine was refluxed over and then distilled from calcium hydride and stored over Linde 4A molecular sieves (dried at 200°). Sodium iodide was dried in the presence of phosphorous pentoxide at room temperature under high vacuum for at least twenty-four hours. Pivlayl chloride was distilled before use.

"Diffusion crystallization" was effected using ether/pentane for blocked intermediates and methanol/ether for the final products. A concentrated solution of the nucleoside (with the final products warming was necessary) in the first mentioned solvent contained in a beaker or small wide mouth erlenmeyer flask was placed in a desiccator containing a large volume of the second solvent, in which the material is insoluble. Crystallization was allowed to proceed at room temperature for from two to five days and the crystals were then collected, without cooling. In no case was it necessary to collect more than two crops, with the first crop generally giving ca. 90% of the material obtained.

Adenosine was purchased from Raylo Chemicals Ltd., Edmonton, Alberta and tubercidin from the Upjohn Company, Kalamazoo, Michigan.

B. SYNTHESES

Reaction of 2',3'-O-methoxyethylideneadenosine (131) with sodium iodide and pivalyl chloride in pyridine. To a solution of 646 mg (0.002 mole) of 131 in 40 ml of pyridine was added 6 g (0.04 mole) of NaI. The vigorously stirred solution was heated to reflux and 2.4 ml (0.02 mole) of pivalyl chloride was added. The reaction was stirred at reflux for 4 minutes, allowed to cool for 20 minutes and 10 ml of methanol was added. The red solution was stirred for ca. 3 hours and poured into 100 ml of an aqueous solution containing 5 g of $NaHCO_3$ and 0.5 g of $Na_2S_2O_3$. The resulting yellow solution was extracted with 100 ml of diethyl ether. This ether phase was washed with three 15 ml portions of water. The main aqueous layer and the first wash were combined and extracted with a second 100 ml portion of ether. This second ether layer was washed with the second and third aqueous washes from above and a fresh 15 ml portion of water. The combined ether phase was evaporated to give a gum which upon successive coevaporations using toluene and 98% ethanol gave 1.38 g of a yellow-brown solid foam. This material was dissolved in ethyl acetate and applied to a carbon column (40 g. 2.2 x 28 cm) packed in ethyl acetate. The column was eluted with 1600 ml of ethyl acetate followed by 500 ml of ethyl acetate:chloroform (1:1). Fractions comprising 200 ml to 1300 ml of eluate yielded 932 mg of a mixture of 150 and 152, those from 1300 ml to 1600 ml yielded 57 mg of a mixture of 150 and 151 and those from 1600 ml to 2000 ml yielded 217 mg of 151. Rechromatography of the 57 mg of 150 and 151 on a small carbon column (4 g, 1.0 x 17 cm) using 140 ml of ethyl acetate followed by 60 ml of ethyl acetate:chloroform 1:1 for elution gave: from 40 ml to 140 ml, 21 mg of 150, and from 140 ml to 200 ml, 29 mg of 151. The total yield of 151 [6-*N*-pivalamido-9-(2-iodo-2-deoxy-5-*O*-pivalyl-3-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-*D*-arabinofuranosyl)purine] is thus 246 mg (16%). An analytical sample of 151 was obtained by percolation of this material in chloroform through a small silica column followed by "crystallization" from ether:pentane which gave an amorphous solid, m.p. 95-97°; uv (MeOH) max 272; 213 nm (ε 18,600; 29,100) min 243 nm (ε 9700), (0.1 *N* NaOH) 275-295; 216 nm (ε 11,900; 30,600) min 248 nm (ε 7800), (0.1 *N* HCl) 282; 218 nm (ε 16,700; 23,500) min 249 nm (ε 7200); nmr ($CDCl_3$, TMS internal) δ 1.18 [s, 9, $CH{=}C(C[CH_3]_3)$-(O-pivalyl)], 1.26 and 1.34 [s and s, 9 and 9, 5'-$OCOC[CH_3]_3$ and CH=C(*t*-Bu)-($OCOC[CH_3]_3$)], 1.41 (s, 9, 6-$NHCOC[CH_3]_3$), 4.17-4.61 (m, 3, $H_{4'}$, $H_{5',5''}$), 4.87 (d of d, $J_{2'-1'}$ = 4.5 Hz, $J_{2'-3'}$ = 2 Hz, 1, $H_{2'}$), 5.62 ("t", $J_{3'-2'}$ = 2 Hz,

$J_{3',4'}$ = 3 Hz, 1, $H_{3'}$), 5.75 [s, 1, CH=C(t-Bu)-(O-pivalyl)], 5.95 (d, $J_{1'-2'}$ = 4.5 Hz, 1, $H_{1'}$), 8.31 (s, 1, H_8), 8.60 (br, 1, 6-NH-pivalyl), 8.76 (s, 1, H_2); mass spectrum calcd. for $C_{32}H_{46}IN_5O_8$, 755.2391; found, 755.2417.

Anal. Calcd. for $C_{32}H_{46}IN_5O_8$: C, 50.86; H, 6.14; I, 16.80; N, 9.27. Found: C, 50.83; H, 6.11; I, 16.65; N, 9.38.

The mixture of **150** and **152**, 953 mg, was dissolved in 5 ml of diethyl ether and crystallized with diffusion of pentane to give 628 mg (42%) in one crop of pure **150** [6-*N*-pivalamido-9-(3-iodo-3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl)-β-*D*-xylofuranosyl)purine]. The mother liquors, containing 319 mg of material, were dissolved in ether and applied to a column of silica gel (40 g, 1.6 x 42 cm), packed in and eluted with ether. Fractions from 95 to 125 ml contained 95 mg of **152** (8%) and from 125 to 255 ml, 174 mg of a mixture of **150** and **152** was obtained. "Diffusion crystallization" of this mixture (ether/pentane) gave 116 mg of pure **150**, in one crop, for a total crystalline yield of 744 mg (49%), m.p. 168-170°; uv (MeOH) max 271; 212 nm (ε 19,000; 32,700) min 243 nm (ε 11,000), (0.1 *N* NaOH) max 275-295; 216 nm (ε 10,300; 29,300) min 248 nm (ε 6,300), (0.1 *N* HCl) max 281; 216 nm (ε 17,100; 29,300) min 251 nm (ε 7,700); nmr

(CDCl$_3$, TMS internal) δ 1.15 [s, 9, CH=C(C[$\underline{\mathrm{CH_3}}$]$_3$)-(O-pivalyl)], 1.25 [s, 18, 5'-OCOC[$\underline{\mathrm{CH_3}}$]$_3$ and CH=C($\underline{t}$-Bu)-(O-COC[$\underline{\mathrm{CH_3}}$]$_3$)], 1.40 (s, 9, 6-NHCOC[$\underline{\mathrm{CH_3}}$]$_3$), 3.90-4.56 (m, 4, $H_{3'}$, $H_{4'}$, $H_{5',5''}$), 5.75 [s, 1, C$\underline{\mathrm{H}}$=C(t=Bu)-(O-pivalyl)], 5.81 ("t", $\underline{J}_{2'-1'}$ = 2.5 Hz, $\underline{J}_{2'-3'}$ = 1.5 Hz, 1, $H_{2'}$), 6.24 (d, $\underline{J}_{1'-2'}$ = 2.5 Hz, 1, $H_{1'}$), 8.50 (br, 1, 6-N$\underline{\mathrm{H}}$-pivalyl), 8.52 (s, 1, H_8), 8.73 (s, 1, H_2); mass spectrum calcd. for $C_{32}H_{46}IN_5O_8$, 755.2391; found, 755.2424.

Anal. Calcd. for $C_{32}H_{46}IN_5O_8$: C, 50.86; H, 6.14; I, 16.80; N, 9.27. Found: C, 50.69; H: 6.36; I, 16.92; N: 9.54.

The yields in this reaction varied with the reaction time, as shown in Figure 3. In each case the quantities and procedures followed were those described above for a four minute reaction. The yields in the other cases were: for 151; 16% (2 min), 15% (4 min), 15% (6 min), 13% (8 min), and 15% (10 min), for the initial crystalline yield of 150 (in the same sequence); 41%, 44%, 38%, 31%, and 29%, for the total yield of 150; 46%, 48%, 45%, 41%, and 37%, and for 152; 2.4%, 4%, 8.8%, 13% and 16%.

The 152 obtained here was identical with a known sample (by nmr and tlc comparison) prepared in the reaction of 150 with silver acetate.

Reaction of 2',3'-*O*-methoxyethylidineadenosine (131) with pivalyl chloride in pyridine at 50°. To a solution of 3.23 g (0.01 mole) of 131 in 100 ml of pyridine heated in an oil bath at 50° was added 12 ml (0.1 mole) of pivalyl chloride. After stirring at 50° for 66 hours the reaction was poured into 300 ml of a saturated $NaHCO_3$ solution and extracted with 200 ml of ether. The ether layer was washed with three 50 ml portions of water. The main aqueous layer and the first wash were combined and extracted with a second 200 ml portion of ether. This ether layer was washed with the second and third aqueous washes from above and a fresh 50 ml portion of water. The combined ether phase was evaporated to a yellow gum which upon successive coevaporations using toluene and 98% ethanol gave a solid foam. Addition of 50 ml of ether resulted in the separation of 1.17 g (22%) of 6-*N*-Pivalamido-9-(2,3-*O*-[4,4-dimethyl-3-oxo-pent-1-enylidene]-5-*O*-pivalyl-β-*D*-ribofuranosyl)purine (138), m.p. 130-131°; uv (MeOH) max 268; 210 nm (ε 37,200; 26,200) min 228 nm (ε 6200); the nmr showed 138 to be a mixture of geometric isomers in the ratio of ca. 7:3, nmr ($CDCl_3$, TMS internal) δ 1.11 (s, 9, C=CHCOC[CH_3]$_3$), 1.15 (s, 9, 5'-OCOC[CH_3]$_3$), 1.38 (s, 9, NH-COC[CH_3]$_3$), 4.25 (m, 2, $H_{5'}$, $H_{5''}$), 4.43 (m, 1, $H_{4'}$), 5.27 (s, 1, C=CH-pivalyl), 5.59 (d of d, $J_{3'-4'}$ = 4 Hz, $J_{3'-2'}$ = 7 Hz, 1, $H_{3'}$), 5.74 (m, 1, $H_{3'}$ of minor isomer), 6.11 (m, 1, $H_{2'}$ of minor isomer), 6.18 (d of d, $\underline{J}_{2'-3'}$ = 7 Hz, $\underline{J}_{2'-1'}$ = 2 Hz, 1, $H_{2'}$), 6.39 (m, 1, $H_{1'}$ of minor isomer), 6.50 (d, $\underline{J}_{1'-2'}$ = 2 Hz, 1, $H_{1'}$), 8.26 (s, 1, H_2), 8.50 (s, 1, H_2 of minor isomer), 8.57 (s, 2, NH_2), 8.64 (s, 1, H_8), 8.67 (s, 1, H_8 of minor isomer).

Anal. Calcd. for $C_{27}H_{37}N_5O_7$: C, 59.65; H, 6.86; N, 12.88. Found: C, 59.64; H, 6.82; N, 12.76.

The mother liquors from the crystallization of 138 were evaporated to give 5.55 g of a yellow solid foam. A 1.0 g sample of this material was dissolved in ether and applied to a silica column (50 g, 2.0 x 44 cm) packed in ether and eluted with: 300 ml of ether; 700 ml of 2.5% methanol in ether; and 500 ml of 5% methanol in ether. From the fractions comprising 200 to 350 ml, 123 mg (10%) of 141 was obtained; from 550 to 650 ml, 33 mg (4%) of 132 was obtained; from 650 to 850 ml, 188 mg (21%) of 134, contaminated with some 132, was obtained; from 1150 to 1500 ml 142 mg (14%) of 138 was obtained, for a total yield of 36% of 138. The 132, 134 and 141 obtained were shown to be identical to known samples by comparison of their nmr and mass spectra, and by identical migration on tlc (silica, 3% methanol in ether).

Reaction of 6-*N*-Pivalamido-9-(2,3-*O*-[4,4-dimethyl-3-oxo-pent-1-enylidene]-5-*O*-pivalyl-β-*D*-ribofuranosyl)-purine (138) with sodium iodide and pivalyl chloride

in pyridine. A 1.09 g (0.002 mole) sample of 138 was reacted with 6 g (0.04 mole) of NaI and 2.4 ml (0.02 mole) of pivalyl chloride in 40 ml of pyridine and the reaction mixture purified identically as described above for the analogous reaction of 0.002 mole of 131. The yields were: 151, 152 mg (15%); 150, 754 mg (50%); 152, 235 mg (15%). Each was found to be identical to an authentic sample by nmr, tlc (silica, ether, developed four times), and for 150 and 152 the melting point and mixed melting point comparison.

Reaction of 150 with 80% acetic acid. A 378 mg (0.0005 mole) sample of 150 was dissolved in 10 ml of 80% acetic acid and the solution stirred in an oil bath at 80° for 24 hours. The solution was then evaporated to dryness and the dark residue triturated with ether and filtered. The ether filtrate was evaporated and gave 300 mg of a brown solid foam, uv max (MeOH) 259 nm; nmr ($CDCl_3$,TMS internal) δ 1.15 [s, 9, CH=C(C[CH_3]$_3$)-(O-pivalyl)], 1.25 [s, 18, 5'-OCOC[CH_3]$_3$ and CH=C(*t*-Bu)-(OCOC[CH_3]$_3$)], 3.85-4.53 (m, 4, $H_{3'}$, $H_{4'}$, $H_{5',5''}$), 5.76 [s, 1, CH=C(t-Bu)-(O-pivalyl)], 5.81 (m, 1, $H_{2'}$), 6.05 (m, 3, $H_{1'}$, 6-NH_2), 8.33 (s, 2, H_2 and H_8).

Reaction of 134 with pivalyl chloride. To a solution of 0.2 g (0.0004 mole) of 134 in 5 ml of pyridine was added 0.033 ml (0.0008 mole) of methanol and 0.5 ml (0.004 mole) of pivalyl chloride. The solution was refluxed for 2 hours, allowed to cool and 5 ml of methanol added. The product, 0.23 g was isolated by extraction as described above for the preparation of 138. Tlc (silica, ether), nmr and mass spectral analysis showed only unreacted 134.

Reaction of 134 with pivalyl chloride and sodium iodide. To a solution of 0.2 g (0.0004 mole) of 134 and 1.2 g (0.008 mole) of sodium iodide in 5 ml of pyridine heated at reflux was added 0.033 ml (0.0008 mole) of methanol and 0.5 ml (0.004 mole) of pivalyl chloride. The solution was refluxed for five minutes, allowed to cool and 5 ml of methanol added. The product, 0.2 g, was isolated by extraction as described above for the preparation of 150 and 151. Tlc (silica, ether), nmr and mass spectral analysis showed only unreacted 134.

Isolation of 2',3'-O-(methoxy pivalylethylidene)-adenosine 148. A 10 g sample of the ether-extractable non-polar material obtained from large scale preparations of 2',3'-anhydroadenosine carried out in this laboratory,[155] was dissolved in 10 ml of 3% methanol in chloroform and applied to a 600 g column of J. T. Baker silica gel. The column was packed in and eluted with 3% methanol in chloroform at a fast flow rate and contained in fractions 1500-3200 ml, 1.31 g of an unidentified mixture, 3200-3700 ml, 3.97 g of mainly one isomer of 148, 3700-3900 ml, 1.50 g of a mixture of isomers of 148, 3900-5100 ml, 3.33 g of mainly the more polar isomer of 148. The 3.97 g fraction of the more non-polar isomer was crystallized from ether to give 1.96 g of this pure isomer, m.p. 162-4°; uv (MeOH) max 259 nm; nmr ($CDCl_3$, TMS internal) δ 1.22 (s, 9, $C[CH_3]_3$), 3.30 (s, 2, $-CH_2-$), 3.38 (s, 3, $-OCH_3$), 4.02 (m, 2, $H_{5',5''}$), 4.63 (m, 1, $H_{4'}$), 5.52 (m, 2, $H_{2'}$, $H_{3'}$), 6.42 (m, 3, $H_{1'}$, $6-NH_2$), 8.06 (s, 1, H_2), 8.45 (s, 1, H_8).

Anal. Calcd. for $C_{18}H_{25}N_5O_6$: C, 53.06; H, 6.19; N, 17,19. Found: C, 52.98; H, 6.24; N, 17.14.

The more polar isomer (3.33 g) was crystallized from acetone to give 1.95 g of the pure isomer, m.p. 184-5°; uv (MeOH) max 259 nm; nmr ($CDCl_3$, TMS internal) δ 1.15 (s, 9, $C[CH_3]_3$), 3.24 (s, 2, $-CH_2-$), 3.55 (s, 3, $-OCH_3$), 3.98 (m, 2, $H_{5',5''}$), 4.66 (m, 1, $H_{4'}$), 5.50 (m, 2, $H_{2'}$, $H_{3'}$), 6.39 (d, $J_{1',2'}$ = 2 Hz, 1, $H_{1'}$), 6.51 (s, 2, $6-NH_2$), 8.03 (s, 1, H_2), 8.44 (s, 1, H_8).

Anal. Found: C, 52.97; H, 6.21; N, 17.34.

The mother liquors from the crystallization of both isomers and the material from the overlapping fractions were combined and evaporated. The residue was dissolved in chloroform and precipitated by dropwise addition to pentane to give after filtration 3.0 g of a 2:1 mixture (by nmr) of the more non-polar to polar isomer.

Reaction of 148 with pivalyl chloride. A. To 1.02 g (0.0025 mole) of 148 (mixed isomers) in 50 ml of pyridine was added 3.0 ml (0.025 mole) of pivalyl chloride and the solution heated at reflux for two hours. After cooling, the mixture was poured into 100 ml of a 10% solution of $NaHCO_3$, stirred for 5 minutes and extracted with 100 ml of ether. This ether layer was washed with two 50 ml portions of water and the extraction and washing was repeated with a second 100 ml portion of ether. The ether layers were combined and evaporated and the residue coevaporated using toluene and 98% ethanol to give 1.5 g of a solid foam. Crystallization of this material from ether gave 355 mg (26%) of 138. Purification of the mother liquors on a silica gel column (51 g, 2.2 x 32 cm) packed in and eluted with ether contained, in fractions comprising 200 to 400 ml, 200 mg (12%) of 141, identified by tlc (silica, ether) nmr and mass spectral comparison. The fractions from 400 to 580 ml contained 50 mg of a mixture of 141 and 149 and from

580 to 1100 ml contained 470 mg (33%) of 149, identified by comparison of nmr and mass spectra with 148 and by conversion to 148 on treatment with sodium methoxide.

B. A 0.12 g (0.0003 mole) sample of 148 in 7.5 ml of pyridine was treated with 0.35 g (0.003 mole) of pivalyl chloride for five hours at reflux. After cooling, 2 ml of methanol was added and the solution stirred overnight. Isolation of the product was carried out by extraction as described above and gave 170 mg of a solid foam. Tlc (silica, ether) showed this material to be a mixture of 141 and 149 in an approximate ratio of 1:3.

Reaction of 148 with pivalyl chloride and sodium iodide. To 0.1 g (0.00025 mole) of 148 and 0.75 g (0.005 mole) of sodium iodide in 10 ml of refluxing pyridine was added 0.3 ml (0.0025 mole) of pivalyl chloride. Heating was continued for six minutes, the reaction allowed to cool and 5 ml of methanol added. After stirring overnight the products, 188 mg, were isolated by extraction as in the preparation of 150 and 151 above. Tlc (silica, ether) showed this material to a mixture of ca. 50% of 149 and 50% 150, 151 and 152.

Reaction of 138 with sodium methoxide in methanol. To 193 mg (0.00035 mole) of 138 dissolved in 5 ml of methanol was added 200 mg of sodium methoxide and the mixture stirred overnight. A separate experiment on a small sample showed that reaction is complete after only ca. four hours at room temperature. The reaction mixture was evaporated, the residue dissolved in 10 ml of water and this solution was extracted with 25 ml of methylene chloride. Evaporation of the methylene chloride layer gave a gum which was triturated with ether and filtered. The residue, 40 mg, was found to be identical with 148 by tlc (silica, 3% methanol in ether) and nmr spectral comparison.

6-*N*-Pivalamido-9-(3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-*D*-*glycero*-pent-3-enofuranosyl)purine (152). 3.78 g (0.005 mole) of 150 and 4.17 g (0.025 mole) of silver acetate were dissolved in 150 ml of pyridine and stirred in a water bath at 15° for ca. 17 hours. The resulting dark solution was poured into 300 ml of 5% $NaHCO_3$. The mixture containing precipitated silver salts was extracted with three 200 ml portions of ether; each was washed with a 50 ml portion of water. The ether extracts were combined and evaporated and the residue coevaporated using toluene and then 98% ethanol. The residue was then dissolved in chloroform and filtered through celite to give, after evaporation, a quantitative yield of 152 as a white solid foam, pure by tlc (silica, ether, developed four times). This material was crystallized from 10 ml of ether using pentane diffusion to give 2.64 g (84%) of pure *152*, m.p. 126-129°; uv (MeOH) max 271; 212 nm (ε 20,000; 41,800) min 243 nm (ε 11,600), (0.1 *N* NaOH) max 278 nm (ε 11,900) min 245 nm (ε 6,500), (0.1 *N* HCl) max 279; 211 nm (ε 19,100; 44,400) min 250 nm (ε 10,200); nmr ($CDCl_3$, TMS internal) δ 1.17 [s, 9, $CH{=}C(C[\underline{CH}_3]_3)$-(O-pivalyl)], 1.22 and 1.30 [s and s, 9 and 9, 5-$OCOC[\underline{CH}_3]_3$ and $CH{=}C$(*t*-Bu)-($OCOC[\underline{CH}_3]_3$)], 1.44 (s, 9, 6-$NHCOC[\underline{CH}_3]_3$), 4.73 (s, 2, $H_{5',5''}$), 5.43 (m, 1, $H_{3'}$), 5.74 [s, 1, $C\underline{H}{=}C$(*t*-Bu)-(O-pivalyl)], 6.08 (m, 1, $H_{2'}$), 6.62 (d, $J_{1'-2'}$ = 2.0 Hz, 1, $H_{1'}$), 8.08 (s, 1, H_8), 8.66 (br, 1, 6-N$\underline{H}$-pivalyl), 8.78 (s, 1, H_2).

Anal. Calcd. for $C_{32}H_{45}N_5O_8$: C, 61.23; H, 7.23; N, 11.16. Found: C, 61.01; H, 6.98; N, 10.98.

6-N-Pivalamido-9-(3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-erythro-pentofuranosyl)purine (155). To 755 mg (0.001 mole) of *150*, 420 mg (0.005 mole) of $NaHCO_3$ and 250 mg of 5% Pd/C was added 10 ml of water and 50 ml of 95% ethanol. The mixture was then hydrogenated at 50 psi for 2 hours. The reaction mixture was filtered through a celite pad and the catalyst washed with 50 ml of 95% ethanol and 50 ml of chloroform. After evaporation of the colorless filtrate, the residue was partitioned between 200 ml of ether and 20 ml of water. The ether layer was washed with a second 20 ml portion of water and evaporated to give 629 mg (quantitative yield) of *155* as a white solid foam. A crystalline sample of *155* was obtained with difficulty from ethanol/water, m.p. 92.5-93.5°; uv (MeOH) max 271; 212 nm (ε 18,500; 33,100) sh 257 nm (ε 12,800) min 242 nm (ε 9,700), (0.1 *N* HCl) max 281; 216 nm (ε 19,600; 30,600) min 248 nm (ε 7,400), (0.1 *N* NaOH) max 275-285 nm (ε 11,100) min 246 nm (ε 6,600); nmr ($CDCl_3$, TMS internal) δ 1.15 [s, 9, $CH{=}C(C[\underline{CH_3}]_3)$-(O-pivalyl)], 1.20 and 1.29 [s and s, 9 and 9, 5'-$OCOC[\underline{CH_3}]_3$ and $CH{=}C$(*t*-Bu)-($OCOC[\underline{CH_3}]_3$)], 1.40 (s, 9, 6-$NHCOC[\underline{CH_3}]_3$), 2.23 (d of d of d, $\underline{J}_{3''-3'}$ = 14 Hz, $\underline{J}_{3''-4'}$ = 6 Hz, $\underline{J}_{3''-2'}$ = 2 Hz, 1, $H_{3''}$), 2.74 (d of d of d, $\underline{J}_{3'-3''}$ = 14 Hz, $\underline{J}_{3'-4'}$ = 10 Hz, $\underline{J}_{3'-2'}$ = 6 Hz, 1, $H_{3'}$), 4.33 (m, 2, $H_{5'}$, $H_{5''}$), 4.54 (m, 1, $H_{4'}$), 5.69 (m, 1, $H_{2'}$), 5.74 [s, 1, $C\underline{H}$=[illegible]*t*-Bu)-(O-pival)], 6.04 (d, $\underline{J}_{1'-2'}$ = 1.5 Hz, 1, $H_{1'}$), 8.09 (s, 1, H_8), 8.53 (s, 1, 6-N$\underline{H}$-pivalyl), 8.76 (s, 1, H_2), 3.30 (s, 1, H_2O).

Anal. Calcd. for $C_{32}H_{47}N_5O_8 \cdot 1/2\ H_2O$: C, 60.17, H, 7.57; N, 10.97. Found: C, 59.94; H, 7.61; N, 11.23.

3'-Deoxyadenosine 18. *Method A.* A 629 mg (0.001 mole) sample of *155* (the solid foam from a 0.001 mole reduction of *150* as described above) was dissolved in 100 ml of methanol:triethylamine:water (45:10:45) and stirred at room temperature for 2 days. Evaporation of the solution to dryness and crystallization of the residue from ca. 20 ml of methanol (with ether diffusion) gave a first crop of 185 mg of *18*. A second crop of 40 mg of *18* was similarly obtained from 5 ml of CH_3OH for a total yield of 225 mg (90%) of crystalline *18*, m.p. 227-230°; $[\alpha]_{\underline{D}}^{26}$ -46.2° (*c* 0.49, H_2O); uv (MeOH) max 258 nm (ε 15,300) min 226 nm (ε 2,700); nmr (DMSO-*d*$_6$, TMS internal) δ 1.95 (d of q, $\underline{J}_{3''-3'}$ = 13 Hz, *J* $\underline{J}_{3''-4'}$ = 6H, $\underline{J}_{3''-2'}$ = 3 Hz, 1, $H_{3''}$), 2.30 ("septet", $\underline{J}_{3'-3''}$ = 13 Hz, $\underline{J}_{3'-4'}$ = 8 Hz, $\underline{J}_{3'-2'}$ = 6Hz, 1, $H_{3'}$), 3.63 (m, 2, $H_{5',5''}$), 4.39 (m, irradiation at 3.63 gives "t", $\underline{J}_{\text{apparent}}$ = 7 Hz, 1, $H_{4'}$), 4.63 (m, 1, $H_{2'}$), 5.19 (t, $\underline{J}_{OH-5',5''}$ = 5.5 Hz, 1, 5'-OH), 5.68 (d, $\underline{J}_{OH-2'}$ = 4.0 Hz, 1, 2'-OH), 5.92 (d, $\underline{J}_{1'-2'}$ = 2.5 Hz, 1, $H_{1'}$), 7.30 (s, 2, NH_2), 8.22 (s, 1, H_2), 8.42 (s, 1, H_8). [reported[109] m.p. 225-226°; $[\alpha]_{\underline{D}}^{23}$ -45.8° (*c* 0.6, H_2O), uv max 258 nm (ε 15,100)].

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.88. Found: C, 48.02; H, 5.29; N, 27.83.

Method B. A 629 mg (0.001 mole) sample of *155* (the foam from a 0.001 mole reduction of *150*) was dissolved in 100 ml of absolute ethanol containing ca. 170 mg of sodium (already dissolved). After 18 hours the solution was neutralized with acetic acid and evaporated to dryness. The white residue was partitioned between 100 ml of pentane and 100 ml of water. The aqueous layer was evaporated to a small volume and applied to a column of Dowex 1-X2 (OH^-) resin (1.3 x 40 cm) packed in water and eluted with 50 ml of water followed by 350 ml of 30% methanol in water. The fractions comprising 100 to 400 ml gave 251 mg (quantitative) of 18. Crystallization from methanol (with ether diffusion) gave a first crop yield of 18 of 214 mg (85%).

6-N-Pivalamido-9-(2-deoxy-5-O-pivalyl-3-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-*erythro*-pentofuranosyl)purine (182). To 755 mg (0.001 mole) of 151, 420 mg (0.005 mole) $NaHCO_3$ and 250 mg of 5% Pd/C was added 10 ml of water and 50 ml of 95% ethanol. The mixture was then hydrogenated at 50 psi for 2 hours. The reaction mixture was filtered through a celite pad and the catalyst washed with 50 ml of 95%, ethanol and 50 ml of chloroform. After evaporation of the colorless filtrate, the residue was partitioned between 80 ml of chloroform and 20 ml of water. Evaporation of the chloroform layer gave a white solid foam which was dissolved in 10 ml of ether. Rapid crystallization of 395 mg of

182 occurred. After filtration the volume of the mother liquors was reduced to 5 ml and an additional 74 mg of 182 separated for a total crystalline yield of 469 mg (75%), m.p. 127-129°; uv (MeOH) max 271; 212 nm (ε 19,700; 35,800), sh 257 nm (ε 13,800), min 242 nm (ε 10,000); (0.1 N NaOH) max 275-285 nm (ε 12,600), min 246 nm (ε 7,600); nmr ($CDCl_3$, TMS, internal), δ 1.18 [s, 9, CH=C(C[$\underline{CH_3}$]$_3$)-(O-pivalyl)], 1.23 and 1.35 [s and s, 9 and 9, 5'-OCOC[$\underline{CH_3}$]$_3$ and CH=C(*t*-Bu)-(OCOC[$\underline{CH_3}$])], 1.42 (s, 9, 6-NHCOC[$\underline{CH_3}$]$_3$, 2.66 (d of d of d, $J_{2''-2'}$ = 14 Hz, $J_{2''-1'}$ = 6 Hz, $J_{2''-3'}$ = 2 Hz, 1, $H_{2''}$), 2.91 (d of d of d, $J_{2'-2''}$ = 14 Hz, $J_{2'-1'}$ = 8 Hz, $J_{2'-3'}$ = 6 Hz, 1, $H_{2'}$), 4.35 (s, 3, $H_{4'}$, $H_{5'}$, $H_{5''}$), 5.40 (m, 1, $H_{3'}$), 5.74 [s, 1, C$\underline{H}$=C(*t*-Bu)-(O-pivalyl)], 6.47 (d of d, $J_{1'-2'}$ = 8 Hz, $J_{1'-2''}$ = 6 Hz, 1, $H_{1'}$), 8.18 (s, 1, H_8), 8.50 (s, 1, 6-N$\underline{H}$-pivalyl), 8.78 (s, 1, H_2).

Anal. Calcd. for $C_{32}H_{47}N_5O_8$: C, 61.03; H, 7.52; N, 11.31. Found: C, 60.75; H, 7.27; N, 11.31.

2'-Deoxyadenosine 5. To 315 mg (0.0005 mole) of 182 was added 200 ml of methanol:triethylamine:water (45:10:45). After stirring for 2 days at room temperature the reaction was evaporated to a gum which was crystallized from 1 ml of methanol (with ether diffusion) to give a first crop of 109 mg (87%), m.p. 192-3°; $[\alpha]_{\underline{D}}^{26}$ -28.0° (*c* 0.991, H_2O); uv (MeOH) max 258 nm (15,300) min 226 nm (3300); nmr (DMSO -$\underline{d}_6$, TMS internal) δ 2.27 (d of q,

$J_{2''-1'}$ = 6 Hz, $J_{2''-3'}$ = 3 Hz, $J_{2''-2'}$ = 13 Hz, 1, $H_{2''}$), 2.75 ("septet", $J_{2'-1'}$ = 8 Hz, $J_{2'-3'}$ = 6 Hz, $J_{2'-2''}$ = 13 Hz, 1, $H_{2'}$), 3.61 (m, 2, $H_{5',5''}$), 3.92 (m, 1, $H_{4'}$), 4.44 (m, 1, $H_{3'}$), 5.29 (m, 2, 5'-OH, 2'-OH), 6.38 (q, $J_{1'-2'}$ = 8 Hz, $J_{1'-2''}$ = 6 Hz, 1, $H_{1'}$), 7.31 (s, 2, NH_2), 8.19 (s, 1, H_2), 8.37 (s, 1, H_8), [reported[63] m.p. 188-190°, $[\alpha]_{D}^{21}$ -26° (*c* 1, H_2O)].

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.88. Found: C, 48.04; H, 5.04; N, 27.64.

6-N-Pivalamido-9-(3-iodo-3-deoxy-5-O-pivalyl)-3-D-xylofuranosyl)purine (161). To a solution of 3.95 g (0.025 mole) of $KMnO_4$ in 50 ml of pyridine and 25 ml of water stirred in an ice bath at 2° was added 3.78 g (0.005 mole) of 150. Stirring was continued at 2° for two hours and 100 ml of 95% ethanol was then added. After an additional 18 hours in the cold, the reaction was filtered through celite and the residue washed with ca. 200 ml of 95% ethanol. The filtrate was then evaporated to a yellow gum. This gum was dissolved in 500 ml of ether and washed with a 50 ml portion of 5% $NaHCO_3$ solution and then two 50 ml portions of water. The ether phase was evaporated to a gum which was coevaporated successively using toluene and then 98% ethanol to give a white solid foam in quantitative yield. This material was dissolved in 50 ml of ether and 2.08 g (76%) of 161 rapidly crystallized. The mother liquors were evaporated, dissolved in 5 ml of ether, and placed in a desiccator containing pentane where another 0.26 g of 161 crystallized for a total crystalline yield of 2.34 g (86%), m.p. 104-105°; uv (MeOH) max 272 nm (ε 18,200) min 233 nm (ε 4500), (0.1 N NaOH) max 292; 222 nm (ε 10,100; 22,500) sh 276 nm (ε 9200) min 247 nm (ε 5300), (0.1N HCl) max 281; 212 nm (ε 19,400; 19,800) min 242 nm (ε 5400); nmr (DMSO-d_6, TMS internal) δ 1.18 (s, 9, 5'-OCOC[CH_3]$_3$), 1.31 (s, 9, 6-NH-COC[CH_3]$_3$), 3.36 (br, 1, 2'-OH), 4.18-4.58 (m, 4, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{5''}$), 5.12 (d of d, $J_{2'-1'}$ = 4.5 Hz, $J_{2'-3'}$ = 5.5 Hz, 1, $H_{2'}$), 5.99 (d, $J_{1'-2'}$ = 4.5 Hz, 1, $H_{1'}$), 8.63 (s, 1, H_8), 8.75 (s, 1, H_2), 10.10 (br, 1, NH-pivalyl).

Anal. Calcd. for $C_{20}H_{28}IN_5O_5$: C, 44.04; H, 5.17; I, 23.27; N, 12.84. Found: C, 44.13; H, 5.27; I, 23.57; N, 12.75.

6-N-Pivalamido-9-(3-iodo-3-deoxy-2-O-mesyl-5-O-pivalyl-β-D-xylofuranosyl)adenine (162). To a solution of 545 mg (0.001 mole) of 161 in 2.5 ml of pyridine, cooled in an ice bath, was added 0.5 ml (0.0065 mole) of mesyl chloride. After two hours the reaction was poured into 100 ml of 5% $NaHCO_3$ and the solution was extracted with 150 ml of ether. The ether layer was washed with two 25 ml portions of water and evaporated to give 605 mg

(97%) of 162 as a yellow foam; uv (MeOH) max 271 nm, min 233 nm; nmr ($CDCl_3$, TMS internal) δ 1.20 (s, 9, 5'-$OCOC[CH_3]_3$), 1.36 (s, 9, 6-$NHCOC[CH_3]_3$), 3.33 (s, 3, OSO_2CH_3), 4.06-4.66 (m, 4, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{5''}$), 5.83 (m, 1, $H_{2'}$), 6.20 (d, $J_{1'-2'}$ = 1.5 Hz, 1, $H_{1'}$), 8.31 (br, 1, NH-pivalyl) 8.39 (s, 1, H_8), 8.71 (s, 1, H_2), ir (nujol) 1175 cm^{-1} (OSO_2R).

6-Amino-9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)purine (46). To 1.09 g (0.002 mole) of 161 in 5 ml of pyridine, cooled in an ice bath, was added 1 ml (0.013 mole) of mesyl chloride and stirring in the ice bath was continued for two hours. The reaction was then poured into an ice cold solution of 25 ml of water containing 1.8 g (0.045 mole) of NaOH and 1.5 g (0.010 mole) of NaI. The reaction was removed from the cold after one hour and stirred for 16 hours at room temperature. The solution was then evaporated to dryness, dissolved in water, and applied in a volume of ca. 25 ml to a column of Dowex 1- x 2 (OH^-) resin (3 x 83 cm). The column was eluted with 600 ml of water followed by 200 ml of 10%, 200 ml of 20% and 900 ml of 30% methanol in water. The fractions from 200 to 550 ml were strongly basic. 414 mg (89%) of 46 was obtained on evaporation of the fractions from 900 to 1900 ml. Crystallization of this material from 200 ml of CH_3OH

(with ether diffusion) gave a first crop of 340 mg of 46 as large prisms. A second crop of 40 mg was similarly obtained from 5 ml of methanol for a total crystalline yield of 380 mg (81%), m.p. 196-200°; resolidifies, 280-310° d; $[\alpha]_{D}^{23}$ +20.6° (*c* 0.394, CH_3OH); uv (MeOH) max 258 nm (ε 15,400) min 226 nm (ε 3,000); nmr (DMSO-d_6, TMS internal) δ 3.64 (m, 2, $H_{5',5''}$; on D_2O exch *d*, $J_{5',5''-4}$ = 3.5 Hz), 4.94 (m, 1, $H_{4'}$), 5.08 (t, $J_{OH-5',5''}$ = 5.5 Hz, 1, 5'-OH), 6.16 (d of q, $J_{3'-2'}$ = 6 Hz, $J_{3'-4'}$ = 2.5 Hz, $J_{3'-1'}$ = 1.5 Hz, 1, $H_{3'}$), 6.49 (d of "t", $J_{2'-3'}$ = 6 Hz, $J_{2'-4'}$ = 1.5 Hz, $J_{2'-1'}$ = 1.5 Hz, 1, $H_{2'}$), 6.98 ("quintet", $J_{1'-2'}$ = 1.5 Hz, $J_{1'-3'}$ = 1.5 Hz, $J_{1'-4'}$ = 3 Hz, 1, $H_{1'}$), 7.28 (s, 2, NH_2), 8.19 (s, 2, H_8, H_2). [reported[111] m.p. 194-195°; uv max 260 nm (ε 15,200); $[\alpha]_{D}^{23}$ 22.8° (*c* 0.25, MeOH)].

Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.49; H, 4.76; N, 30.03. Found: C, 51.50; H, 4.67; N, 30.06.

6-Amino-9-(3-deoxy-β-D-glycero-pent-3-enofuranosyl)-purine (156). *Method A*. To 1.26 g (0.002 mole) of 152 dissolved in 20 ml of methanol was added 0.5 g of $NaOCH_3$. The reaction was stirred at room temperature overnight, evaporated to dryness, dissolved in 100 ml of water/25 ml of 95% ethanol, and filtered through celite. After reducing the volume to ca. 100 mg, 400 ml of 156 crystallized. A second crop of 60 mg was obtained by concentration of the mother liquors. A total crystalline yield of 460 mg (92%) was obtained, m.p. 227-330°; $[\alpha]_{D}^{26}$ -354° (c 0.388, H_2O/DMF, 1:1); uv (MeOH) max 258 nm (ϵ 15,000) min 230 nm (ϵ 3500); nmr (DMSO-d_6, internal TMS) δ 4.03 (d, $J_{5',5''-OH}$ = 5.5 Hz, 2, $H_{5',5''}$), 5.26 (m, 3, $H_{2'}$, $H_{3'}$, 5'-OH), 5.75 (d, $J_{OH-2'}$ = 5.5 Hz, 1, 2'-OH), 6.27 (d, $J_{1'-2'}$ = 2.0 Hz, 1, $H_{1'}$), 7.33 (s, 2, NH_2), 8.17 and 8.21 (s and s, 1 and 1, H_2 and H_8) [reported[111] m.p. 240-241°; uv max (MeOH) 258 nm (ϵ 15,000); $[\alpha]_D$ 307° (c 0.1, H_2O)].

Anal. Calcd. for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.01; H, 4.68; N, 28.32.

Method B. 1.26 g (0.002 mole) of **152** was dissolved in 300 ml of methanol:triethylamine:water (45:10:45) and the solution stirred at room temperature for 24 hours. The reaction was then evaporated to dryness and the residue triturated with ether, filtered and the filtrate discarded. The residue was dissolved in 100 ml of water/25 ml of CH_3OH and the volume was reduced to ca. 100 ml. Crystallization then occurred giving a first crop of 400 mg of **156**. Concentration of the mother liquors gave a second crop of 35 mg for a total crystalline yield of 435 mg (87%) of **156**.

3'-Deoxyadenosine (18) and 6-amino-9-(3-deoxy-α-L-threo-pentofuranosyl)purine (61). A mixture of 249 mg

(0.001 mole) of *156*, 250 mg of 10% Pd/C, 25 ml of water and 25 ml of 95% ethanol was hydrogenated at 10 psi for two hours. The mixture was then filtered through a celite pad, the catalyst washed with 30 ml of 95% ethanol, and the filtrate evaporated to give 240 mg of a white powder. This powder was dissolved in 30% methanol in water and applied to a column of Dowex 1-X2 (OH^-) resin (2.4 x 95 cm), packed and eluted with 30% methanol in water. The fractions from 2300 to 3000 ml contained 133 mg (53%) of *18*. Crystallization of this material from methanol (with ether diffusion) gave a first crop of 104 mg $[\alpha]_{\underline{D}}^{26}$ -47.2° (c 0.506, H_2O), identical with a known sample (see above) by nmr and tlc (silica, 10% methanol in ether).

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.88. Found: C, 47.73; H, 5.48; N, 27.77.

The fractions from 4900 to 6000 ml contained 86 mg (35%) of *61*. Crystallization of this material from methanol (with ether diffusion) gave a first crop of 70 mg, m.p. 241-5° $[\alpha]_{\underline{D}}^{26}$ -68.2° (c 0.544, H_2O); uv (MeOH) max 258 nm (ε 15,700) min 227 nm (ε 2900); nmr (DMSO-$\underline{d}_6$, TMS internal) δ 1.85 ("quintet", $\underline{J}_{3''-3'}$ = 13 Hz, $\underline{J}_{3''-2'}$ = 6 Hz, $\underline{J}_{3''-4'}$ = 8 Hz, 1, $H_{3''}$), 2.45 (m, partially obscured by DMSO, $\underline{J}_{3'-4'}$ = 7 Hz, $\underline{J}_{3'-3''}$ = 13 Hz, 1, $H_{3'}$), 3.52 ("t", $\underline{J}_{apparent}$ = 5Hz, on D_2O exch d, $\underline{J}_{5',5''-4'}$ = 4.5 Hz, 2, $H_{5'}$, $H_{5''}$), 4.50 (m, irradiation at 3.52 gives "t", $\underline{J}_{apparent}$ = 7 Hz, 1, $H_{4'}$), 4.90 (m, on D_2O exch "quintet",

$J_{2'-1'}$ ≅ 4 H, $J_{2'-3'}$ ≅ $J_{2'-3''}$ = 6.5 Hz, 2, $H_{2''}$, 5'-OH), 5.43 (d, $J_{2',OH-2'}$ = 5 Hz, 1, 2'-OH), 5.90 (d, $J_{1'-2'}$ = 4 Hz, 1, $H_{1'}$), 7.26 (s, 2, NH_2), 8.19 (s, 1, H_2), 8.30 (s, 1, H_8). [reported[94] $[\alpha]_D^{25}$ -52° (*c* 0.5, H_2O); uv max (95% EtOH) 260 nm (ε 13,100)].

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; 4, 5.21; N, 27.88. Found: C, 47.65; H, 5.27; N, 28.05.

6-*N*-Pivalamido-9-(5-pivaloxymethyl-2-furanyl)purine (153). A 627 mg (0.001 mole) sample of 152 was heated in an oil bath at 180° for three minutes. After cooling the residue was dissolved in chloroform and evaporated to a gum. The gum was dissolved in 10 ml of ether from which a first crop of 289 mg (73%) of 153 rapidly crystallized. Concentration of the mother liquors gave a second crop of 15 mg for a total crystalline yield of 304 mg (76%), m.p. 141-143°; uv (MeOH) max 261; 212 nm (ε 26,200; 18,900) min 228 nm (ε 14,400), (0.1 *N* NaOH) max 292; 230 nm (ε 13,400; 18,700) sh 248 nm (ε 14,900) min 277 nm (ε 12,400), (0.1 *N* HCl) max 276; 207 nm (ε 25,400; 21,900) sh 255 nm (ε 17,800) min 228 nm (ε 11,900); nmr ($CDCl_3$, TMS internal) δ 1.19 (s, 9, 5'-$OCOC[CH_3]_3$), 1.40 (s, 9, 6-$NHCOC[CH_3]_3$), 5.08 (s, 2, $H_{5',5''}$), 6.57 (d, $J_{3'-2'}$ = 4 Hz, 1, $H_{3'}$), 6.77 (d, $J_{2'-3'}$ = 4 Hz, 1, $H_{2'}$), 8.34 (s, 1, H_8), 8.57 (br, 1, 6-NH-pivalyl), 8.81 (s, 1, H_2).

Anal. Calcd. for $C_{20}H_{25}N_5O_4$: C, 60.13; H, 6.31; N, 17.54. Found: C, 60.02; H, 6.49; N, 17.66

6-Amino-9-(5-hydroxymethyl-2-furanyl)purine (157).

To 798 mg (0.002 mole) of 153 dissolved in 20 ml of methanol was added 250 mg of $NaOCH_3$. The mixture was stirred at room temperature for 17 hours and evaporated to dryness. The residue was triturated with 25 ml of water and filtered. The filter cake was washed with water until the filtrate was neutral (ca. 15 ml) and then with methanol and ether to give 432 mg (92%) of 157 as a white solid, m.p. 253-255° d; uv (MeOH) max 247 nm (ε 23,000) sh 280 nm (ε 8000) min 218 nm (ε 14,000), (0.1 *N* HCl) max 250 nm (ε 25,800) sh 226 nm (ε 13,000) min 212 nm (ε 11,000), (0.1 *N* NaOH) max 249 nm (ε 21,800); nmr (DMSO-d_6, TMS internal) δ 4.44 (d, $J_{5'-OH}$ = 5.5 Hz, 2, $H_{5',5''}$), 5.31 (t, $J_{OH-5'}$ = 5.5 Hz, 1, 5'-OH), 6.49 (d, $J_{3'-2'}$ = 3 Hz, 1, $H_{3'}$), 6.64 (d, $J_{2'-3'}$ = 3 Hz, 1, $H_{2'}$), 7.41 (s, 2, 6-NH_2), 8.21 (s, 1, H_2), 8.40 (s, 1, H_8).

Anal. Calcd. for: $C_{10}H_9N_5O_2$: C, 51.94; H, 3.92; N, 30.29. Found: C, 52.10; H, 3.89; N, 30.26.

6-*N*-Pivalamido-9-(5-methyl-2-furanyl)purine (168).

A mixture of 798 mg (0.002 mole) of 153, 336 mg (0.004 mole) of $NaHCO_3$, 400 mg of 5% Pd/C, 10 ml of water and

50 ml of 95% ethanol was hydrogenated at 10 psi for one hour. The mixture was then filtered through celite, and the catalyst was washed with 10 ml of water, 25 ml of ethanol and 50 ml of chloroform. After evaporation of the filtrate, the residue was partitioned between 10 ml of water and 50 ml of chloroform. The water layer was extracted with two 50 ml portions of chloroform and the combined chloroform layers were washed with 25 ml of water and evaporated to give 580 mg of a white solid foam. This material was dissolved in chloroform and applied to a column of silica gel (25 g, 2.2 x 12.5 cm) packed in and eluted with chloroform. Evaporation of the fractions from 50 to 315 ml gave 490 mg (82%) of pure 168 as a white foam. Crystallization was effected using ethanol/water giving a first crop of 260 mg, of 168 m.p. 109-111°; uv (MeOH) max 262; 210 nm (ϵ 26,400; 23,000) min 228 nm (ϵ 13,500), (0.1 N NaOH) max 288; 229 nm (ϵ 14,600; 18,500) sh 248 nm (ϵ 14,200) min 276 nm (ϵ 13,500), (0.1 N HCl) max 277; 218 nm (ϵ 29,500; 26,400) sh 255 nm (ϵ 17,500)min 232 nm (ϵ 10,500); nmr ($CDCl_3$, TMS internal) δ 1.40 (s, 9, NH-COC[$\underline{CH_3}$]$_3$), 2.35 (s, 3, CH_3), 6.14 (m, 1, $H_{3'}$), 6.57 (d, $\underline{J}_{2'-3'}$ = 3 Hz, 1, $H_{2'}$), 8.25 (s, 1, H_2), 8.81 (s, 1, H_8), 8.55 (br, 1, N$\underline{H}$-pivalyl).

Anal. Calcd. for $C_{15}H_{17}N_5O_2$: C, 60.18; H, 5.73; N, 23.40. Found: C, 60.43; H, 5.82; N, 23.38.

6-Amino-9-(5-methyl-2-furanyl)purine (158). A 150 mg (0.0005 mole) sample of 168 was dissolved in 100 ml of methanol:triethylamine:water (45:10:45) and stirred at room temperature for two days. The solution was then evaporated to dryness and the residue crystallized from 10 ml of methanol to give a first crop of 95 mg (88%) of 158 m.p. 238-239°; uv (MeOH) max 248 nm (ε 23,000) sh 280 nm (ε 7,400) min 220 nm (ε 12,800), (0.1 N HCl) max 251 nm (ε 26,000) min 217 nm (ε 9900), (0.1 N NaOH) max 251 nm (ε 22,200); nmr (DMSO-d_6, TMS internal) δ 2.35 (s, 3, CH_3), 6.29 (m, 1, $H_{3'}$), 6.57 (d, $J_{2'-3'} = 3$ Hz, 1, $H_{2'}$), 7.41 (s, 2, 6-NH_2), 8.21 (s, 1, H_2), 8.38 (s, 1, H_8). [reported[81] m.p. 236-237°; uv max (MeOH) 249 nm (20,000)].

Anal. Calcd. for $C_{10}H_9N_5O$: C, 55.81; H, 4.21; N, 32.55. Found: C, 56.03; H, 4.37; N, 32.43.

6-Amino-9-(2,3-dideoxy-β-DL-glycero-pentofuranosyl)-purine (20 and 169). A mixture of 231 mg (0.001 mole) of 157, 252 mg (0.003 mole) of $NaHCO_3$, 460 mg 10% Pd/C, 10 ml of water and 40 ml of methanol was hydrogenated at 60 psi for 30 hours. The mixture was then filtered through celite, and the catalyst washed with 50 ml of methanol. The filtrate was evaporated to dryness, dissolved in water and applied to a column of Dowex 1- X 2 (OH^-) resin

(1.3 x 37 cm) packed in water. The column was eluted with 70 ml of water followed by 120 ml of 30% methanol in water and 500 ml of 0.1 *M* NH_4HCO_3. The fractions comprising 20 to 50 ml were strongly basic, those from 70 to 150 ml gave 149 mg (64%) of 20 and 169 and those from 530 ml to 690 ml contained 18 mg (by uv) of adenine. Crystallization of a 75 mg sample of 20 and 169 from methanol gave a first crop of 52 mg, m.p. 165-167°; uv (MeOH) max 258 nm (ε 15,900) min 226 nm (ε 2900); nmr (DMSO-d_6, TMS internal) δ 2.08 (m, 2, $H_{3',3''}$), 2.41 (m, 2, $H_{2',2''}$), 3.59 (m, 2, $H_{5',5''}$), 4.10 ("septet", $J_{4'-5',5''} = J_{4'-3'} = J_{4'-3''}$ = 7.0 Hz, 1, $H_{4'}$), 5.04 (t, $J_{OH-5',5''}$ = 5.5 Hz, 1, 5'-OH), 6.22 (t, $J_{1'-2',2''}$ = 5.0 Hz, 1, $H_{1'}$), 7.23 (s, 2, 6-NH_2), 8.16 (s, 1, H_2), 8.36 (s, 1, H_8). The nmr and mass spectra of a sample of pure 20, prepared by hydrogenation of 46,[81] were identical with the spectra obtained for this racemate (20 and 169). Treatment of a small sample of the racemate with toluenesulfonyl chloride, followed by heating in acetone gave quantitative cyclonucleoside formation[17] (tlc) and gave a product with uv max (H_2O) 273.

Anal. Calcd. for $C_{10}H_{13}N_5O_2$: C, 51.05; H, 5.57; N, 29.77. Found: C, 50.93; H, 5.80; N, 29.66.

6-N-Pivalamido-9-(2-iodo-2-deoxy-5-O-pivalyl-β-D-arabinofuranosyl)purine (164). To a solution of 790 mg

(0.005 mole) of $KMnO_4$ in 10 ml of pyridine and 5 ml of water stirred in an ice bath at 2° was added 755 mg (0.001 mole) of 151. Stirring was continued at 2° for two hours and 20 ml of 95% ethanol was then added. After an additional 16 hours in the cold, the reaction was filtered through celite, and the residue was washed with ca. 50 ml of 95% ethanol. The filtrate was evaporated to a yellow gum. This gum was dissolved in 100 ml of ethyl acetate and washed with 10 ml of 5% $NaHCO_3$ followed by two 10 ml portions of water. The ethyl acetate layer was evaporated to a white powder, and then was triturated with ether and filtered to give 410 mg (75%) of 164. Recrystallization of a sample of this material from methanol gave 164 as a hydrate, m.p. 216-217° dec.; uv (MeOH) max 272; 211 nm (ε 17,400; 19,000) min 231 nm (ε 3600), (0.1 N NaOH) 280-300; 215 nm (ε 10,600; 16,100) min 244 nm (ε 5700), (0.1 N HCl) 282; 213 nm (ε 18,900; 17,800) min 238 nm (ε 4100); nmr ($CDCl_3$, TMS internal) δ 1.18 (s, 9, 5'-OCOC$[\underline{CH_3}]_3$), 1.31 (s, 9, 6-NHCOC$[\underline{CH_3}]_3$), 3.95 (br m, 1, $H_{4'}$), 4.43 (m, 2, $H_{5',5''}$), 4.78 (m, 2, $H_{2'}$, $H_{3'}$), 6.16 (m, 1, 3'-OH), 6.45 (d, $J_{1'-2'}$ = 4.8 Hz, 1, $H_{1'}$), 8.55 (s, 1, H_8), 8.60 (br, 1, 6-N$\underline{H}$-pivalyl), 8.72 (s, 1, H_2), 3.30 (s, 2, H_2O).

Anal. Calcd. for $C_{20}H_{28}IN_5O_5{\cdot}H_2O$: C, 42.64; H, 5.37; I, 22.53; N, 12.35. Found: C, 42.87; H; 5.39; I, 22.71; N, 12.35.

6-*N*-Pivalamido-9-(2-iodo-2-deoxy-3-*O*-trimethylsilyl-5-*O*-pivalyl-β-D-arabinofuranosyl)purine (165). To a stirred solution of 55 mg (0.0001 mole) of 164 in 2 ml of pyridine was added 0.1 ml of *N*,*O*-bis-(trimethylsilyl)-acetamide (BSA). The solution was stirred at room temperature for 50 minutes and an additional 0.05 ml of BSA added. After a further 30 minutes 1 ml of methanol was added and the solution immediately evaporated to dryness. The residue was dissolved in 50 ml of ether and washed with three 10 ml portions of water. Evaporation of the ether layer gave 94 mg of a gum which was dissolved in chloroform and applied to a silica column (2.5 g, 0.8 x 13.5 cm) packed in and eluted with chloroform. Evaporation of the fractions comprising 8 to 20 ml gave 59 mg (95%) of 165 as a white solid foam; uv (CH_3CN) max 272; 212 nm (ε 272/ε 212 = 0.88), min 237 nm (ε 272/ε 237 = 4.92); nmr ($CDCl_3$, TMS internal) δ 0.24 (s, 9, $Si[CH_3]_3$), 1.27 (s, 9, 5'-$OCOC[CH_3]_3$), 1.41 (s, 9, 6-$NHCOC[CH_3]_3$), 4.11 (m, 1, $H_{4'}$), 4.47 ("d"; $J_{apparent}$ = 4.5 Hz, 2, $H_{5',5''}$), 4.66"q", $J_{2'-1'}$ = 5.5 Hz, $J_{2'-3'}$ = 4.5 Hz, 1, $H_{2'}$), 4.84 ("t", $J_{3'-2'}$ = $J_{3'-4'}$ = 4.5 Hz, 1, $H_{3'}$), 6.11 (d, $J_{1'-2'}$ = 5.5 Hz, 1, $H_{1'}$), 8.25 (s, 1, H_8), 8.35 (s, 1, 6-N*H*-pivalyl), 8.78 (s, 1, H_2); mass spectrum calculated for $C_{23}H_{36}IN_5O_5Si$: 617.1531, found: 617.1506.

6-N-Pivalamido-9-(2-deoxy-5-O-pivalyl-D-erythro-pent-1-enofuranosyl)purine (166). To a stirred solution of 165 mg (0.0003 mole) of 164 dissolved in 6 ml of pyridine was added 0.3 ml of *N*-*O*-bis-(trimethylsilyl)-acetamide (BSA). The solution was stirred at room temperature for 45 minutes and an additional 0.3 ml of BSA was added. After a further 45 minutes, 0.3 ml of diazabicyclo-[4.3.0]-nonene-5 (DBN) was added. Stirring was continued for 90 minutes and 4 ml of methanol was added. After an additional 30 minutes, the reaction was evaporated to a gum which was dissolved in 50 ml of ethyl acetate and washed with two 10 ml portions of water. The aqueous layers were then back extracted with a 50 ml portion of ethyl acetate. Evaporation of the ethyl acetate layers gave 140 mg of residue which was dissolved in chloroform and applied to a silica column (2.8 g, 0.8 x 15 cm) packed in and eluted with chloroform. The fractions comprising 35 to 165 ml were evaporated to give 123 mg (98%) of 166 as a gel-like solid; uv (MeOH) max 264; 248 nm (ε 18,600; 19,200) sh 216 nm (ε 15,900) min 257; 227 nm (ε 18,500; 13,200), (0.1 *N* NaOH) max 288, 232 nm (ε 12,700; 17,100) min 267 nm (ε 10,700); nmr ($CDCl_3$, TMS internal) δ 1.21 (s, 9, 5'-OCOC[CH_3]$_3$), 1.31 (s, 9, 6-NHCOC[CH_3]$_3$), 4.32 (m, 2, $H_{5',5''}$), 4.69 (m, 1, $H_{4'}$), 4.92 (m, 1, $H_{3'}$), 5.57 (d, $J_{OH-3'}$ = 6.0 Hz, 1, 3'-OH), 5.82 (d, $J_{2'-3'}$ = 2.8 Hz, 1, $H_{2'}$), 8.60 (br, 1, 6-NH-pivalyl), 8.56 (s, 1, H_8), 8.86 (s, 1, H_2). Mass spectrum of the 3'-O-trimethylsilyl derivative of 166 calcd. for $C_{23}H_{35}N_5O_5Si$, 489.2407; found, 489.2425.

Anal. Calcd. for C_{2}[illegible]$H_{27}N_5O_5$: C, 57.54; H, 6.52; N, 16.78. Found: C, 5[illegible].85; H, 6.68; N, 16.42.

6-Amino-9-(2-deoxy-D-erythro-pent-1-enofuranosyl)-purine (159). To a stirred solution of 1.13 g (0.002 mole, as hydrate) of 164 in 20 ml of pyridine was added 1.0 ml of N-O-bis-(trimethylsilyl)-acetamide (BSA). The solution was stirred at room temperature for 60 minutes and an additional 1.0 ml of BSA added. After a further 60 minutes, 1.0 ml of diazabicyclo-[4.3.0]-nonene-5 (DBN) was added. Stirring was continued for two hours and 10 ml of methanol added. After an additional 30 minutes the reaction was evaporated to a gum which was dissolved in 200 ml of ethyl acetate and washed with four 20 ml portions of water. The aqueous layers were successively back extracted with a 100 ml portion of ethyl acetate, and the combined ethyl acetate layers evaporated. The residue was dissolved in 20 ml of methanol and 500 mg of $NaOCH_3$ was added. After stirring overnight at room temperature, the mixture was evaporated and the residue dissolved in 25 ml of water. Crystallization occurred rapidly and gave a first crop of 460 mg of 159 as the hydrate. A second crop of 14 mg was obtained on concentration of the mother liquors for a total crystalline yield of 474 mg (89%, as the hydrate) of 159 m.p. 196-198°, resolidifies at ca. 202-210° and melts with decomposition at 224-235°; $[\alpha]_D^{27}$ 100.5° (*c* 0.96, DMF); uv (MeOH) max 250 nm (ε 16,500) sh 281; 290 nm (ε 7200; 4700) min 222 nm (ε 10,700), (0.1 *N* NaOH) max 251 nm (ε 16,400) sh 279; 290 nm (ε 6200; 3300) min 221 nm (ε 10,600); nmr (DMSO-$\underline{d}_6$, TMS internal) δ 3.59 ("t", $\underline{J}_{\mathrm{apparent}}$ = 6 Hz, 2, $H_{5',5''}$), 4.43 ("sextet", $\underline{J}_{4'-5',5''}$ = 5.0 Hz, $\underline{J}_{4'-3'}$ = 3.0 Hz, 1, $H_{4'}$), 4.84 ("quintet", $\underline{J}_{3'-2'}$ = 2.8 Hz, $\underline{J}_{3'-4'}$ = 3.0 Hz, $\underline{J}_{3'-3'-OH}$ = 6.0 Hz, 1, $H_{3'}$), 5.03 (t, $\underline{J}_{5'-OH-5',5''}$ = 6.0 Hz, 1, 5'-OH), 5.35 (d, $\underline{J}_{3'-OH-3'}$ = 6.0 Hz, 1, 3'-OH), 5.69 (d, $\underline{J}_{2'-3'}$ = 2.8 Hz, 1, $H_{2'}$), 7.47 (s, 2, 6-NH_2), 8.30 and 8.34 (s and s, 1 and 1, H_2 and H_8); mass spectrum calcd. for $C_{10}H_9N_5O_2$ (M^+ -H_2O), 231.0756; found, 231.0752; tris-(trimethylsilyl) derivative of 159, Calcd. for $C_{19}H_{35}N_5O_3Si_3$, 465.2047; found, 465.2062; spectrophotometrically determined pka ∿ 3.31.

Anal. Calcd. for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.28; H, 4.74; N, 27.92.

2'-Deoxyadenosine (5) and 6-amino-9-(2-deoxy-α-D-erythro-pentofuranosyl)purine (167). A mixture of 267 mg (0.001 mole, as hydrate) of 159, 84 mg (0.001 mole) of $NaHCO_3$, 100 mg of 5% Pd/c, 10 ml of water and 40 ml of 95% ethanol was hydrogenated at 3 psi for two hours. The mixture was then filtered through celite, the catalyst washed with 25 ml of ethanol and 25 ml of water, and the filtrate evaporated. The residue was dissolved in water and applied to a column of Dowex 1-X2 (OH^-) resin (2.2 x 58 cm) packed in and eluted with water. Evaporation of the fractions from 1650 to 2050 ml gave 34 mg (14%) of 167. Crystallization of this product from CH_3OH/with ether diffusion gave a first crop of 30 mg, m.p. 216-217°; $[\alpha]_D^{23}$ 70.8° (c 0.92, H_2O), uv (MeOH) max 258 nm (ε 15,100) min 226 nm (ε 2900); nmr (DMSO-d_6, TMS internal) δ 2.31 (d of "t", $J_{2'-2''}$ = 14 Hz, $J_{2''-3'}$ = 3 Hz, $J_{2''-1'}$ = 3 Hz, 1, $H_{2''}$), 2.72 ("sextet", $J_{2'-2''}$ = 14 Hz, $J_{2'-3'}$ = 7 Hz, $J_{2'-1'}$ = 8 Hz, 1, $H_{2'}$), 3.46 ("t", $J_{apparent}$ = 5 Hz, on D_2O exch d, $J_{5',5''-4'}$ = 4.5 Hz, 2, $H_{5'}$, $H_{5''}$), 4.12 (m, 1, $H_{4'}$), 4.30 (m, 1, $H_{3'}$), 4.81 (t, $J_{OH-5',5''}$ = 5 Hz, 1, 5'-OH), 5.75 (d, $J_{OH-3'}$ = 4.5 Hz, 1, 3'-OH), 6.33 (q, $J_{1'-2'}$ = 8 Hz, $J_{1'-2''}$ = 3 Hz, 1, $H_{1'}$), 7.22 (s, 2, NH_2), 8.16 (s, 1, H_2), 8.38 (s, 1, H_8). [reported[162] 211-213.5°; $[\alpha]_D^{27}$ 69.8° (c 0.9, H_2O); uv max (H_2O) 259.5 nm (ε 15,500)].

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.88. Found: C, 47.79; H, 5.10; N, 28.04.

Evaporation of the fractions comprising 2350 to 4050 ml gave 181 mg (68%, as the hydrate) of 5. Crystallization of this material from methanol (with ether diffusion) gave a first crop of 143 mg, m.p. 192-193°, $[\alpha]_D^{23}$ -26.7° (c 1.10, H_2O) and an nmr spectrum identical with that of an authentic sample (see above).

Anal. Calcd. for $C_{10}H_{13}N_5O_3 \cdot H_2O$: C, 44.60; H, 5.65; N, 26.01. Found: C, 44.79; H, 5.48; N, 25.78.

4-N-Pivalamido-7-(3-iodo-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)-pyrrolo[2,3-d]pyrimidine (171). To a solution of 644 mg (0.002 mole) of 170[143] in 40 ml of pyridine was added 6 g (0.04 mole) of NaI. The vigorously stirred solution was heated to reflux and 2.4 ml (0.02 mole) of pivalyl chloride was added. The reaction was heated at reflux for 4 minutes, allowed to cool for 20 minutes, and 10 ml of methanol was added. The red solution was stirred for ca. 3 hours and poured into 100 ml of an aqueous solution containing 5 g of $NaHCO_3$ and 0.5 g of $Na_2S_2O_3$. The resulting yellow solution was extracted with 100 ml of ether. This ether phase was washed with three 15 ml portions of water. The main aqueous layer and the first wash were combined and extracted with a second 100 ml portion of ether. This second ether layer was washed with the second and third aqueous washes from above and a fresh 15 ml portion of water. The combined ether phase was evaporated to give a gum which upon successive coevaporations using toluene and 98% ethanol gave 1.38 g of a yellow solid foam. This material was dissolved in ethyl acetate and applied to a carbon column (40 g, 2.2 x 28 cm) packed in ethyl acetate and eluted with chloroform:ethyl acetate (1:1). The fractions comprising 100 to 500 ml contained 987 mg (64%) of 171 as a white solid foam containing only a trace amount of 172 by tlc (silica, 20% pentane in ether). An analytically pure sample of 171 was obtained by chromatography of a 500 mg sample of this product on a silica gel column (52 g, 2.2 x 31 cm) packed in ether:pentane (1:1) and eluted with 275 ml of ether:pentane (1:1) followed by 225 ml of 25% pentane in ether. Evaporation of the fractions from 350 to 500 ml gave 380 mg of pure 171 as a white solid foam, uv (MeOH) max 287; 219 nm (ϵ 8,700; 45,600) sh 229 nm (ϵ 29,800) min 256 nm (ϵ 5600), (0.1 *N* HCl) max 291; 222 nm (ϵ 11,700; 40,300) min 263 nm (ϵ 9,900), (0.1 *N* NaOH) max 285-305; 243 nm (ϵ 10,600; 29,900) sh 232 nm (ϵ 27,300) min 268 nm (ϵ 10,000); nmr ($CDCl_3$, TMS internal) δ 1.11 [s, 9, CH=C(C[CH_3]$_3$)-(O-pivalyl], 1.21 and 1.23 [s and s, 9 and 9, 5'-OCOC[CH_3]$_3$ and CH=C(*t*-Bu)-(OCOC[CH_3]$_3$], 1.35 (s, 9, 4-NHCOC[CH_3]$_3$), 3.88 (m, 1, $H_{4'}$), 4.32 (m, 3, $H_{3'}$, $H_{5'}$, $H_{5''}$), 5.69 (d of d, $J_{2'-1'}$ = 3.5 Hz, $J_{2'-3'}$ = 2 Hz, 1, $H_{2'}$), 5.74 [s, 1, CH=C(*t*Bu)-(O-pivalyl)], 6.53 (d, $J_{1'-2'}$ = 3.5 Hz, 1, $H_{1'}$), 7.10 (d, J_{5-6} = 4 Hz, 1, H_5), 7.64 (d, J_{6-5} = 4 Hz, 1, H_6), 8.23 (s, 1, 4-NH-pivalyl), 8.50 (s, 1, H_2).

Anal. Calcd. for $C_{33}H_{47}IN_4O_8$: C, 52.52; H, 6.28;

I, 16.82; N, 7.43. Found: C, 52.45; H, 6.40; I, 16.98; N, 7.37.

4-*N*-Pivalamido-7-(3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-*D*-*glycero*-pent-3-enofuranosyl)pyrrolo[2,3-*d*]pyrimidine (172). A 1.51 g (0.002 mole) portion of 171 and 1.67 g (0.01 mole) of silver acetate were dissolved in 60 ml of pyridine and stirred in a water bath at 16° for ca. 19 hours. The resulting dark solution was poured into 120 ml of 5% aqueous $NaHCO_3$. The mixture, containing precipitated silver salts, was extracted with 200 ml of ether and the ether washed with three 20 ml portions of water. The main aqueous layer and the first wash were combined and extracted with 200 ml portions of ether. This ether layer was washed with the second and third aqueous washes from above and a fresh 20 ml portion of water. The combined ether phase was evaporated and successively coevaporated using toluene and then 98% ethanol. The residue was dissolved in chloroform, filtered through celite, and evaporated to give 1.3 g of a brown solid foam. This material was dissolved in 25% pentane in ether and applied to a silica gel column (75 g, 2.2 x 46 cm) packed in and eluted with 25% pentane in ether. The fractions comprising 150 to 270 ml were evaporated to give 1.26 g (quantitative yield) of *172* as a white solid foam, uv (MeOH) max 287; 218 nm (ε 9000; 50,500) sh 230 nm (ε 32,000) min 254 nm (ε 5,200), (0.1 *N* HCl) max 288; 222 nm (ε 11,800; 35,600) min 261 nm (ε 9600), (0.1 *N* NaOH) max 285-300; 238 nm (ε 12,100; 32,100) sh 225 nm (ε 27,900) min 267 (ε 10,700); nmr ($CDCl_3$, TMS internal) δ 1.15 [s, 9, $CH=C(C[\underline{CH_3}]_3)$-(O-pivalyl)], 1.22 and 1.28 [s and s, 9 and 9, 5'-$OCOC[\underline{CH_3}]_3$ and $CH=C$(*t*-Bu)-$(OCOC[\underline{CH_3}]_3)$], 1.39 (s, 9, 4-$NHCOC[\underline{CH_3}]_3$), 4.70 (s, 2, $H_{5',5''}$), 5.38 (m, 1, $H_{3'}$), 5.74 [s, 1, $C\underline{H}=C$(*t*-Bu)-(O-pivalyl)], 5.94 (m, 1, $H_{2'}$), 6.94 (d, $J_{1'-2'}$ = 2.0 Hz, 1, $H_{1'}$), 7.02 (d, J_{5-6} = 4.0 Hz, 1, H_5), 7.12 (d, J_{6-5} = 4.0 Hz, 1, H_6), 8.57 (s, 1, 4-N$\underline{H}$-pivalyl), 8.89 (s, 1, H_2).

Anal. Calcd. for $C_{33}H_{46}N_4O_8$: C, 63.24; H, 7.40; 8.94. Found: C, 63.26; H, 7.60; N, 8.84.

4-Amino-7-(3-deoxy-β-D-glycero-pent-3-enofuranosyl)-pyrrolo[2,3-d]pyrimidine (173). To 1.26 g (0.002 mole) of *172* dissolved in 20 ml of methanol was added 0.5 g of $NaOCH_3$. The reaction was stirred overnight at room temperature and evaporated to dryness. The residue was dissolved in water, applied to a column of Dowex 1-X2 (OH^-) resin (1.3 x 16 cm), and eluted with 650 ml of water followed by 300 ml of 30% methanol in water. Evaporation of the fractions comprising 300 to 950 ml gave 376 mg (75%) of 173. Crystallization of this material from methanol (with ether diffusion) gave a first crop of 257 mg, m.p. 196-198°; $[\alpha]_D^{26}$ -413° (*c* 0.119, H_2O), -457° (*c* 0.984, DMF); uv (MeOH) max 268 nm (ε 13,900) min 238 nm (ε 3100), (H_2O) max 268 nm (ε 13,500) min 239 nm (ε 3300), (0.1 *N* HCl) max 270; 226 nm (ε 12,700; 27,900) min 246 nm (ε 5400), (0.1 *N* NaOH) max 268 nm (ε 13,400) min 240 nm (ε 3700); nmr (DMSO-d_6, TMS internal) δ 3.99 (d, $J_{5',5''-OH}$ = 5.5 Hz, 2, $H_{5'}$, $H_{5''}$), 5.03 (m, 1, $H_{2'}$), 5.20 (m, 2, $H_{3'}$, 5'-OH), 5.64 (d, $J_{OH-2'}$ = 6 Hz, 1, 2'-OH), 6.45 (d, $J_{1'-2'}$ = 2.5 Hz, 1, $H_{1'}$), 6.64 (d, J_{5-6} = 3.5 Hz, H_5), 7.04 (m, 3, 4-NH_2, H_6), 8.07 (s, 1, H_2).

Anal. Calcd. for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.43; H, 5.05; N, 22.46.

3'-Deoxytubercidin (174) and 4-amino-7-(3-deoxy-α-L-threo-pentofuranosyl)pyrrolo[2,3-d]pyrimidine (175). A 248 mg (0.001 mole) sample of 173, 250 mg of 10% Pd/C, 25 ml of water and 25 ml of 95% ethanol were hydrogenated at 10 psi for two hours. The mixture was then filtered through celite, the catalyst was washed with 25 ml of water and 25 ml of ethanol, and the filtrate evaporated. The residue was dissolved in 30% methanol in water and applied to a column of Dowex 1-X2 (OH^-) resin (2.4 x 95 cm), packed in and eluted with 30% methanol in water.

Evaporation of fractions from 2100 to 2900 ml gave 94 mg (38%) of 174. Crystallization of this product from methanol (with ether diffusion) gave a first crop of 80 mg, m.p. 182-183°; $[\alpha]_D^{26}$ -73.4° (c, 0.930, 95% EtOH); uv (MeOH) max 269 nm (ε 11,400) min 239 nm (ε 2700), (0.1 N HCl) max 272; 227 nm (ε 10,700; 24,000) min 246 nm (ε 4300), (0.1 N NaOH) max 270 nm (ε 11,200) min 240 nm (ε 3000); nmr (DMSO-d_6, TMS internal) δ, 1.89 (d of q, $J_{3''-3'}$ = 13 Hz, $J_{3''-2'}$ = 6.5 Hz, $J_{3''-4'}$ = 4 Hz, 1, $H_{3''}$), 2.19 ("septet", $J_{3'-3''}$ = 13 Hz, $J_{3'-2'}$ = 8 Hz, $J_{3'-4'}$ = 6 Hz, 1, $H_{3'}$), 3.56 (m, 2, $H_{5'}$, $H_{5''}$), 4.33 (m, 2, $H_{2'}$, $H_{4'}$), 5.05 (t, $J_{OH-5',5''}$ = 5.5 Hz, 1, 5'-OH), 5.50 (d, $J_{OH-2'}$ = 5.5 Hz, 1, 2'-OH),6.01 (d, $J_{1'-2'}$ = 3 Hz, 1, $H_{1'}$), 6.57 (d, J_{5-6} = 4 Hz, 1, H_5), 6.98 (s, 2, NH_2), 7.32 (d, J_{6-5} = 4 Hz, 1, H_6), 8.09 (s, 1, H_2), [reported[106] m.p. 180-181°; $[\alpha]_D^{27}$ -75.1° (c, 1, EtOH); uv (MeOH) max 269 nm (ε 11,700)].

Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.78; H, 5.66; N, 22.12.

Evaporation of the fractions from 4800 to 6300 ml gave 133 mg (53%) of 175. Crystallization of this solid from methanol (with ether diffusion) gave a first crop of 102 mg, m.p. 191-193°; $[\alpha]_D^{26}$ -80.0° (c 0.725, 95% EtOH); uv (MeOH) max 269 nm (ε 11,200) min 239 nm (ε 2600), (0.1 N HCl) max 271; 227 nm (ε 10,300; 23,500) min 246 nm (ε 4200), (0.1 N NaOH) max 269 nm (ε 10,700) min 239 (ε 2700); nmr (DMSO-d_6, TMS internal) δ 1.82 ("quintet", $J_{3''-3'}$ = 13 Hz, $J_{3''-4'}$ = 7 Hz, $J_{3''-2'}$ = 5 Hz, 1, $H_{3''}$), 2.34 (m, partially obscured by DMSO peak, $J_{3'-4'}$ = $J_{3'-2'}$ = 6 Hz, 1, $H_{3'}$), 3.51 ("t", $J_{apparent}$ = 5 Hz, 2, $H_{5',5''}$), 4.39 (m, 1, $H_{4'}$), 4.66 (m, 1, $H_{2'}$), 4.92 (t, $J_{OH-5',5''}$ = 5.5 Hz, 1, 5'-OH), 5.52 (d, $J_{OH-2'}$ = 5.5 Hz, 1, 2'-OH), 6.05 (d, $J_{1'-2'}$ = 4 Hz, 1, $H_{1'}$), 6.60 (d, J_{5-6} = 4 Hz, 1, H_5), 6.97 (s, 2, 4-NH_2), 7.14 (d, J_{6-5} = 4 Hz, 1, H_6), 8.90 (s, 1, H_2).

Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.78; H, 5.37; N, 22.09.

4-N-Pivalamido-7-(5-pivaloxymethyl-2-furanyl)pyrrolo[2,3-d]pyrimidine (176). A 626 mg (0.001 mole) sample of 176 was heated in an oil bath at 180° for two minutes. After cooling, the residue was dissolved in chloroform and evaporated to a yellow powder. Ether (15 ml) was added and the mixture was filtered to give a first crop of 130 mg of 176. Concentration of the mother liquors gave an additional 150 mg in three crops for a total yield of 280 mg (70%) of small white crystals of 176, m.p. 159-160°; uv (MeOH) max 262; 218 nm (ε 28,600; 24,300) sh 290 nm (ε 8400) min 233 nm (ε 12,700), (0.1 N NaOH) sh 280; 248 nm (ε 15,400; 20,000), (0.1 N HCl) max 286; 235 nm (ε 24,900; 17,500) sh 265 nm (ε 21,300), min 245; 220 nm (ε 15,400; 15,400); nmr ($CDCl_3$, TMS internal) δ 1.16 (s, 9, $OCOC[CH_3]_3$), 1.33 (s, 9, $-NHCOC[CH_3]_3$), 5.03 (s, 2, $H_{5',5''}$), 6.49 (d, $J_{3'-2'}$ = 3 Hz, 1, $H_{3'}$), 6.68 (d, $J_{2'-3'}$ = 3 Hz, 1, $H_{2'}$), 7.14 (d, J_{5-6} = 4 Hz, 1, H_5), 7.50 (d, J_{6-5} = 4 Hz, 1, H_6), 8.20 (br, 1, N*H*-pivalyl), 8.56 (s, 1, H_2).

Anal. Calcd. for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 63.37; H, 6.87; N, 13.92.

4-N-Pivalamido-7-(5-methyl-2-furanyl)pyrrolo[2,3-d]pyrimidine (180). A 100 mg (0.00025 mole) sample of *176*, 84 mg (0.001 mole) of $NaHCO_3$, 100 mg of 5% Pd/C, 10 ml of water and 40 ml 95% ethanol were hydrogenated at 3 psi for 3 minutes. The mixture was then filtered through celite and the catalyst washed with 30 ml of methanol and 30 ml of chloroform. After evaporation of the filtrate, the residue was partioned between 20 ml of water and 50 ml of chloroform. The water layer was extracted with three 10 ml portions of chloroform and the combined chloroform layers were evaporated to give 81 mg of a yellow gum. This gum was dissolved in ether and applied to a silica gel column (10 g, 1.3 x 20 cm) packed in and eluted with ether. Upon evaporation of the fractions comprising 20 to 50 ml, 61 mg (82%) of *180* crystallized, m.p. 127-128°; uv (MeOH) max 262; 217 nm (ε 22,800; 28,100) sh 295 nm (ε 7400) min 238 nm (ε 13,200), (0.1 *N*

HCl) max 286; 235 nm (ε 20,600; 19,300) sh 265 nm (ε 15,300) min 250; 221 nm (ε 12,000; 14,900), (0.1 *N* NaOH) sh 285; 250; 228 nm (ε 12,000; 14,300; 19,400); nmr ($CDCl_3$, TMS internal) δ 1.38 (s, 9, NH-COC[$\underline{CH_3}$]$_3$), 2.33 (d, $J_{CH_3-3'}$ = 1 Hz, 3, CH_3), 6.07 (d of q, $J_{3'-CH_3}$ = 1 Hz, $J_{3'-2'}$ = 3 Hz, 1, $H_{3'}$), 6.49 (d, $J_{2'-3'}$ = 3 Hz, 1, $H_{2'}$), 7.11 (d, J_{5-6} = 4 Hz, 1, H_5), 7.41 (d, J_{6-5} = 4 Hz, 1, H_6), 8.30 (br, 1, N$\underline{H}$-pivalyl), 8.56 (s, 1, Hz).

Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.66; H, 6.21; N, 18.82.

4-Amino-7-(5-methyl-2-furanyl)pyrrolo[2,3-d]pyrimidine (181). A 150 mg (0.0005 mole) sample of 180 was dissolved in 100 ml of methanol:triethylamine:water (45:10:45) and stirred at room temperature for two days. The solution was then evaporated to dryness and the residue crystallized from 5 ml of methanol (with ether diffusion) to give a first crop of 66 mg of 181. The mother liquors were evaporated to dryness and the residue dissolved in 3% methanol in chloroform and applied to a column of silica gel (3 g, 0.8 x 16 cm) packed in and eluted with 3% methanol in chloroform. Upon evaporation of the fractions comprising 10 to 30 ml, 36 mg of 181 crystallized, for a total yield of 102 mg (94%), m.p. 127-130°; uv (MeOH) max 248 nm (ε 25,000) sh 285 nm

(ε 9400) min 223 nm (ε 16,200), (0.1 *N* HCl) max 253; 221 nm (ε 23,000; 15,100) min 232 nm (ε 13,300), (0.1 *N* NaOH) max 246 nm (ε 20,900) sh 232; 280 nm (ε 16,800; 10,300); nmr (DMSO-$\underline{d}_6$, TMS internal) δ 2.26 (d, $\underline{J}_{\mathrm{CH_3-3'}}$ = 1 Hz, 3, $\mathrm{CH_3}$), 6.18 (d of q, $\underline{J}_{\mathrm{3'-CH_3}}$ = 1 Hz, $\underline{J}_{3'-2'}$ = 3 Hz, 1, $\mathrm{H_{3'}}$), 6.43 (d, $\underline{J}_{2'-3'}$ = 3 Hz, 1, $\mathrm{H_{2'}}$), 6.73 (d, $\underline{J}_{5-6}$ = 4 Hz, 1, $\mathrm{H_5}$), 7.17 (br, 2, $\mathrm{NH_2}$), 7.54 (d, $\underline{J}_{6-5}$ = 4 Hz, 1, $\mathrm{H_6}$), 8.11 (s, 1, $\mathrm{H_2}$), 1.07 (t, $\underline{J}$ = 7 Hz, 0.75, $\mathrm{OCH_2\underline{CH_3}}$), 2.94 (q, $\underline{J}$ = 7 Hz, 0.5, $\mathrm{O\underline{CH_2}CH_3}$).

Anal. Calcd. for $\mathrm{C_{11}H_{10}N_4O \cdot 1/4\ Et_2O}$: C, 61.92; H, 5.41; N, 24.07. Found: C, 61.80; H, 5.44; N, 24.12.

4-Amino-7-(5-hydroxymethyl-2-furanyl)pyrrolo[2,3-d]-pyrimidine (177). To 796 mg (0.002 mole) of *176* dissolved in 20 ml of methanol was added 250 mg of $\mathrm{NaOCH_3}$. The mixture was stirred at room temperature for 18 hours and evaporated to dryness. The residue was triturated with 15 ml of water and filtered. The filter cake was washed with water until the filtrate was neutral (*ca.* 15 ml) and then with methanol and ether to give 426 mg (91%) of *177* in two crops, m.p. 178-180°; uv (MeOH) max 249 nm (ε 28,500) sh 285 nm (ε 10,300) min 223 nm (ε 15,700), (0.1 *N* HCl) max 252 nm (ε 26,400) sh 230 nm (ε 16,100), (0.1 *N* NaOH) max 247 nm (ε 24,200) sh 233; 280 nm (ε 18,700; 10,900); nmr (DMSO-$\underline{d}_6$, TMS internal) δ 4.40 (s, 2, $\mathrm{\underline{CH_2}OH}$), 5.25 (br, 1, $\mathrm{CH_2O\underline{H}}$), 6.42 (d, $\underline{J}_{3'-2'}$ = 3.5 Hz, 1, $\mathrm{H_{3'}}$), 6.54

(d, $J_{2'-3'}$ = 3.5 Hz, 1, $H_{2'}$), 6.77 (d, J_{5-6} = 4 Hz, 1, H_5), 7.17 (s, 2, NH_2), 7.40 (d, J_{6-5} = 4 Hz, 1, H_6), 8.16 (s, 1, H_2).

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.11; H, 4.26; N, 24.28.

4-Amino-7-(2,3-dideoxy-β-DL-glycero-pentofuranosyl)-pyrrolo[2,3-d]pyrimidine (178 and 179). A mixture of 230 mg (0.001 mole) of 178, 250 mg (0.003 mole) of $NaHCO_3$, 460 mg of 10% Pd/C, 10 ml of water and 40 ml of methanol was hydrogenated at 60 psi for 16 hours. The mixture was then filtered through celite and the catalyst washed with 50 ml of methanol. The filtrate was evaporated to dryness, dissolved in water, and applied to a column of Dowex 1-X2 (OH^-) resin (1.3 x 43 cm) packed in water and eluted with 60 ml of water followed by 90 ml of 30% methanol in water. Evaporation of the fractions from 40 to 140 ml gave 181 mg (77%) of 178 and 179. Crystallization of this material from methanol (with ether diffusion) gave a first crop of 90 mg, m.p. 70-73°; uv (MeOH) max 270 nm (ε 11,400) min 240 nm (ε 2700), (0.1 N HCl) max 272; 227 nm (ε 10,600; 24,000) min 246 nm (ε 4100), (0.1 N NaOH) max 270 nm (ε 11,000) min 239 (ε 2700); nmr (DMSO-d_6, TMS internal) δ 2.03 (m, 2, $H_{3'}$, $H_{3''}$), 2.26 (m, 2, $H_{2'}$, $H_{2''}$), 3.52 (m, 2, $H_{5'}$, $H_{5''}$), 4.04 (m, 1, $H_{4'}$), 4.96 (m, 1, 5'-OH), 6.33 ("t", $\underline{J}_{\mathrm{apparent}}$ = 6 Hz, 1, $H_{1'}$), 6.56 (d, $\underline{J}_{5-6}$ = 3.5 Hz, 1, H_5), 6.95 (s, 2, 4-NH_2), 7.32 (d, $\underline{J}_{6-5}$ = 3.5 Hz, 1, H_6), 8.05 (s, 1, H_2).

(The nmr spectrum reported[107] for 178 is in agreement with that of this racemate.) Treatment of a small sample of this racemate with toluenesulfonyl chloride followed by heating in acetone to effect cyclonucleoside formation proceeded quantitatively (tlc) and gave a product having uv max (H_2O) 293 nm, sh 273 nm.[66]

Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.22; H, 6.10; N, 23.71.

Ethyl-4,4-dimethyl-3-pivaloxypent-2-enoate (154).

Method A. To 49 g (0.33 mole) of NaI in 250 ml of pyridine was added 39 ml (0.33 mole) of pivalyl chloride followed by the dropwise addition of 20 ml (0.11 mole) of triethylorthoacetate over 15 minutes. The reaction was stirred for one hour and 50 ml of methanol was added. After standing for two days at room temperature the reaction was poured into 500 ml of water containing 30 g of $NaHCO_3$ and 5 g of $Na_2S_2O_3$. This mixture was extracted with 300 ml of pentane and the pentane layer washed with three 100 ml portions of water. The pentane layer was then distilled. A 3.03 g (11%) fraction of 154 was collected at 82-84° (0.1 mm). A pure sample was obtained by crystallization of the solidified material from pentane, to give crystals with m.p. 36-37°; uv (MeOH) max 216 (ϵ 12,800), (0.1 *N* HCl) max 216 nm (ϵ 11,800); nmr ($CDCl_3$, TMS internal) δ 1.13 [s, 9, $CH{=}C(C[C\underline{H_3}]_3)$-(O-pivalyl)], 1.24 (t, *J* = 7.2 Hz, 3, $OCH_2C\underline{H_3}$), 1.34 (s, 9, CH=C(*t*Bu)-$OCOC[C\underline{H_3}]_3$), 4.07 (q, *J* = 7.2 Hz, 2, $O\underline{CH_2}CH_3$), 5.62 [s, 1, $\underline{CH}$=C(*t*Bu)-(O-pivalyl)]; ir (neat) cm^{-1} 1760 ($C{-}C{-}O\underline{CO}C[CH_3]_3$), 1722 (EtO$\underline{CO}$C=C), 1645; 842 (C=C).

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.60; H, 9.42.

Method B. Evaporation of the pentane layer from the preparation of 18, Method B above, gave 232 mg of an oil which was crystallized from pentane to give a first crop of 122 mg (50%) of 154, m.p. 35-36°. The nmr, ir, and mass spectra of 154 prepared by Method A above are identical to those of 154 from this procedure.

REFERENCES

1. P. A. Levene and W. A. Jacobs, *Ber.*, *42*, 2475 (1909).
2. A. Bendich, in "The Nucleic Acids," E. Chargaff and J. N. Davidson, Eds., Vol. I, Academic Press, New York, 1955, Chapter 3.
3. P. A. Levene and L. E. Bass, "Nucleic Acids," Chemical Catalog Co., New York, 1931.
4. R. S. Tipson, *Advan Carbohyd. Chem.*, *1*, 193 (1945).
5. G. R. Barker, *Advan. Carbohyd. Chem.*, *11*, 285 (1956).
6. H. G. Zachau, *Angew. Chem., Int. Ed. Engl.*, *8*, 711 (1969).
7. R. H. Hall, "The Modified Nucleosides in Nucleic Acids," Columbia University Press, New York, 1971.
8. P. A. Levene, *J. Biol. Chem.*, *63*, 653 (1925).
9. P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, *104*, 385 (1934).
10. J. M. Gulland, E. R. Holiday and T. F. Macrae, *J. Chem. Soc.*, 1639 (1934).
11. J. M. Gulland and E. R. Holiday, *J. Chem. Soc.*, 765 (1936).
12. J. M. Gulland and L. F. Story, *J. Chem. Soc.*, *259*, 692 (1938).

13. P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, *94*, 809 (1932); *97*, 491 (1932); *101*, 529 (1933).

14. D. M. Brown and B. Lythgoe, *J. Chem. Soc.*, 1990 (1940).

15. B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 592 (1944).

16. J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 833 (1946).

17. V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

18. J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967, 1685 (1948).

19. J. Baddiley, in "The Nucleic Acids," E. Chargaff and J. N. Davidson, Eds., Vol. I, Academic Press, New York, 1955, Chapter 4.

20. J. A. Montgomery and J. H. Thomas, *Advan. Carbohyd.* Chem., *14*, 283 (1959).

21. J. J. Fox and I. Wempen, *Advan. Carbohyd. Chem.*, *17*, 301 (1962).

22. A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides," Academic Press, New York, 1963.

23. C. A. Dekker and L. Goodman in "The Carbohydrates," 2nd ed., Vol. II A, W. Pigman and D. Horton, Ed., Academic Press, New York, 1970, Chapter 29.

24. L. Toji and S. S. Cohen, *Proc. Nat. Acad. Sci. U.S.*, *63*, 871 (1969).

25. L. Toji and S. S. Cohen, J. Bacteriol., 103, 323 (1970).

26. J. J. Fox, K. A. Watanabe, and A. Bloch, in "Progress in Nucleic Acid Research and Molecular Biology," J. N. Davidson and W. E. Cohn, Eds., Vol. 5, Academic Press, N.Y., 1966, p. 251.

27. K. G. Cunningham, S. A. Hutchinson, W. Manson, and F. S. Spring, J. Chem. Soc., 2299 (1951).

28. H. R. Bentley, K. G. Cunningham, and F. S. Spring, J. Chem. Soc., 2301 (1951).

29. J. U. Nef, Justus Liebigs Ann. Chem., 376, 1 (1910).

30. R. A. Raphael and C. M. Roxburgh, J. Chem. Soc., 3405 (1955).

31. E. A. Kaczka, E. L. Dulaney, C. O. Gitterman, H. B. Woodruff, and K. Folkers, Biochem. Biophys. Res. Commun., 14, 452 (1964).

32. E. A. Kaczka, N. R. Trenner, B. Arison, R. W. Walker and K. Folkers, Biochem. Biophys. Res. Commun., 14, 456 (1964).

33. S. Hanessian, D. C. DeJongh, and J. A. McCloskey, Biochim. Biophys. Acta, 117, 480 (1966).

34. H. Klenow, Biochim. Biophys. Acta, 76, 347 (1963).

35. W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, J. Amer. Chem. Soc., 83, 1906 (1961).

36. Parke, Davis and Company, Belgium Pat. 671,557 (1967).

37. R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, 1970.

38. H. T. Shigeura and G. E. Boxer, *Biochem. Biophys. Res. Commun.*, *17*, 758 (1964).

39. H. T. Shigeura and C. N. Gordon, *J. Biol. Chem.*, *240*, 806 (1965).

40. J. G. Cory, R. J. Suhadolnik, B. Resnick, and M. A. Rich, *Biochim. Biophys. Acta*, *103*, 646 (1965).

41. R. L. Momparler, *Biochem. Biophys. Res. Commun.*, *34*, 465 (1969).

42. A. Kornberg and M. R. Atkinson, private communication to R. J. Suhadolnik, reported in reference 37, p. 150.

43. M. Sprinzl and F. Cramer, *Nature New Biology*, *245*, 3 (1973).

44. M. J. Robins, R. A. Jones, and M. MacCoss, Biochemistry, *13*, 553 (1974).

45. D. Ringer and S. Chládek, *Biochem. Biophys. Res. Commun.*, *56*, 760 (1974).

46. H. Yünsten, H. Yonehara, and H. Vi, *J. Antibiotics (Tokyo)*, *7A*, 113 (1954).

47. H. Yünsten, K. Ohkuma, Y. Ishii, and H. Yonehara, *J. Antibiotics (Tokyo)*, *9A*, 195 (1956).

48. H. Yünsten, *J. Antibiotics (Tokyo)*, *11A*, 233 and 244 (1958).

49. M. J. Robins and R. A. Jones, *J. Org. Chem.*, *39*, 113 (1974).

50. H. Hoeksema, G. Slomp, and E. E. van Tamelen, *Tetrahedron Lett.*, 1787 (1964).

51. H. P. Schnebli, D. L. Hill, and L. L. Bennett, Jr., *J. Biol. Chem.*, *242*, 1997 (1967).

52. C. G. Smith, L. M. Reineke, H. Harpootlian, *Proc. Amer. Assoc. Cancer Res.*, *7*, 259 (1966).

53. D. C. Ward, A. Cerami, E. Reich, N. Mendelsohn, and G. Acs, reported in reference 37, pp. 342-345.

54. A. M. Kapuler, D. C. Ward, N. Mendelsohn, H. Klett, G. Acs, and S. Spiegelman, *Federation Proc.*, *28*, 731 (1969).

55. A. M. Kapuler, D. C. Ward, N. Mendelsohn, H. Klett, and G. Acs, *Virology*, *37*, 701 (1969).

56. A. J. Guarino "in Antibiotics," D. Gottlieb and P. D. Shaw, Eds., Springer Verlag, New York, 1967, p. 468.

57. R. J. Suhadolnik in "Antibiotics," D. Gottlieb and P. D. Shaw, Eds., Springer Verlag, New York, 1967, p. 400.

58. J. J. K. Novák and F. Štorm, *Coll. Czech. Chem. Commun.*, *27*, 902 (1962).

59. J. Škoda, I. Bartošek, and F. Štorm, *Coll. Czech. Chem. Commun.*, 27, 906 (1962).

60. G. L. Eichhorn and P. Clark, *J. Amer. Chem. Soc.*, *85*, 4020 (1963).

61. R. B. Simpson, J. Amer. Chem. Soc., 86, 2059 (1964).

62. A. Todd and T. L. V. Ulbricht, J. Chem. Soc., 3275 (1960).

63. C. D. Anderson, L. Goodman, and B. R. Baker, J. Amer. Chem. Soc., 3967 (1959).

64. M. J. Robins and R. K. Robins, J. Amer. Chem. Soc., 86, 3585 (1964).

65. W. Jahn, Chem. Ber., 98, 1705 (1965).

66. K. Anzai and M. Matsui, Bull. Chem. Soc. Japan, 46, 618 (1973).

67. G. Kowallik, K. Gaertner, G. Etzold, and P. Langen, Carbohyd. Res., 12, 301 (1970).

68. M. Ikehara, H. Tada, and K. Muneyama, Chem. Pharm. Bull. (Tokyo), 13, 639 (1965).

69. M. Ikehara and H. Tada, J. Amer. Chem. Soc., 87, 606 (1965).

70. M. Ikehara and H. Tada, Chem. Pharm. Bull. (Tokyo), 15, 94 (1967).

71. M. Ikehara, Accounts. Chem. Res., 2, 47 (1969).

72. J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., 35, 2319 (1970).

73. J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., 35, 2868 (1970).

74. R. F. Dods and J. S. Roth, J. Org. Chem., 34, 1627 (1969).

75. K. Kikugawa and M. Ichino, Tetrahedron Lett., 87 (1971).

76. K. Kikugawa and M. Ichino, J. Org. Chem., 37, 285 (1972).

77. M. M. Ponpipom and S. Hanessian, Carbohyd. Res., 18, 342 (1971).

78. K. Haga, M. Yoshikawa, and T. Kato, Bull. Chem. Soc. Japan, 43, 3922 (1970).

79. J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., 37, 2289 (1972).

80. L. M. Lerner, J. Org. Chem., 37, 477 (1972).

81. J. R. McCarthy, Jr., M. J. Robins, L. B. Townsend, and R. K. Robins, J. Amer. Chem. Soc., 88, 1549 (1966).

82. J. P. Horwitz, J. Chua, and M. Noel, Tetrahedron Lett., 1343 (1966).

83. J. P. Horwitz, J. Chua, M. A. DaRooge, M. Noel, and I. L. Klundt, J. Org. Chem., 31, 205 (1966).

84. A. F. Russell and J. G. Moffatt, Biochemistry, 8, 4889 (1969).

85. K. Anzai and M. Matsui, Agr. Biol. Chem., 37, 345 (1973).

86. E. J. Corey and R. A. E. Winter, J. Amer. Chem. Soc., 85, 2677 (1963).

87. W. V. Ruyle, T. Y. Shen, and A. A. Patchett, J. Org. Chem., 30, 4353 (1965).

88. J. R. McCarthy, Jr., R. K. Robins, and M. J. Robins, J. Amer. Chem. Soc., 90, 4993 (1968).

89. I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffatt, J. Amer. Chem. Soc., 93, 4323 (1971).

90. J. P. H. Verheyden and J. G. Moffatt, J. Amer. Chem. Soc., 88, 5684 (1966).

91. M. J. Robins, J. R. McCarthy, Jr., and R. K. Robins, J. Heterocycl. Chem., 4, 313 (1967).

92. G. H. Jones and J. G. Moffatt, Abstracts, 158th National Meeting of the American Chemical Society, New York, N.Y., Sept. 1969; U.S. Patent 3,457,255 (1969); Chem. Abstr., 72, 3727 (1970).

93. P. Howgate, A. S. Jones, and J. R. Tittensor, Carbohyd. Res., 12, 403 (1970).

94. K. L. Nagpal and J. P. Horwitz, J. Org. Chem., 36, 3743 (1971).

95. J. Žemlička, J. V. Freisler, R. Gasser, and J. P. Horwitz, J. Org. Chem., 38, 990 (1973).

96. J. Žemlička, R. Gasser, J. V. Freisler, and J. P. Horwitz, J. Amer. Chem. Soc., 94, 3213 (1972).

97. G. Kowollik, K. Gaertner, and P. Langen, Tetrahedron Lett., 1737 (1971).

98. S. Hanessian and N. R. Plessas, J. Org. Chem., 34, 1035 (1969).

99. S. Hanessian and N. R. Plessas, J. Org. Chem., 34, 1045 (1969).

100. S. Hanessian and N. R. Plessas, J. Org. Chem., 34, 1053 (1969).

101. M. M. Ponpipom and S. Hanessian, Can. J. Chem., 50, 246, (1972).

102. M. M. Ponpipom and S. Hanessian, Can. J. Chem., 50, 253 (1972).

103. S. Greenberg and J. G. Moffatt. Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., March - April 1968, C 054; A. F. Russell, S. Greenberg, and J. G. Moffatt. Abstracts, 158th National Meeting of the American Chemical Society, New York, N.Y., Sept. 1969, CARB 014.

104. A. R. Mattocks, J. Chem. Soc., 1918, (1964).

105. A. R. Mattocks, J. Chem. Soc., 4840 (1964).

106. M. J. Robins, J. R. McCarthy, Jr., R. A. Jones, and R. Mengel, Can. J. Chem., 51, 1313 (1973).

107. T. C. Jain, A. F. Russell, and J. G. Moffatt, J. Org. Chem., 38, 3179 (1973).

108. S. Greenberg and J. G. Moffatt, J. Amer. Chem. Soc., 95, 4016 (1973).

109. A. F. Russell, S. Greenberg, and J. G. Moffatt, J. Amer. Chem. Soc., 95, 4025 (1973).

110. T. C. Jain and J. G. Moffatt, Abstracts, 165th National Meeting of the American Chemical Society, Dallas, Tex., April 1973, CARB 15.

111. T. C. Jain, I. D. Jenkins, A. F. Russell, J. P. H. Verheyden, and J. G. Moffatt, J. Org. Chem., 39, 30 (1974).

112. R. Mengel and M. J. Robins, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March - April, 1971, Abstract CARB-002.

113. M. J. Robins, R. Mengel, and R. A. Jones, Abstracts of the VIth International Symposium on Carbohydrate Chemistry (IUPAC), Madison, Wis., Aug. 14-18, p. 41 (1972).

114. M. J. Robins, R. Mengel, and R. A. Jones, J. Amer. Chem. Soc., 95, 4074 (1973).

115. S. Winstein and R. E. Buckles, J. Amer. Chem. Soc., 64, 2780 (1942).

116. H. Meerwein, G. Hinz, D. Hoffman, E. Konig, and E. Pfeil, J. Prakt. Chem., 147, 257 (1937); 154, 83 (1939).

117. H. Meerwein and K. Wunderlich, Angew. Chem., 69, 481 (1957).

118. H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, Justus Liebigs Ann. Chem., 632, (1960).

119. C. B. Anderson, E. C. Fredrich, and S. Winstein, Tetrahedron Lett., 2037 (1963).

120. R. M. Roberts, J. Corse, R. Boschan, D. Seymour, and S. Winstein, J. Amer. Chem. Soc., 80, 1247 (1958).

121. L. R. Schroeder, J. Chem. Soc. (B)., 1789 (1970).

122. K. Freudenberg and H. Scholz, Chem. Ber., 63, 1969 (1930).

123. P. Brigl, Z. physiol. Chem., 116, 1 (1921).

124. C. V. Pittman, Jr., S. P. McManus, and J. W. Larsen, Chem. Rev., 72, 357 (1972).

125. H. Perst, "Oxonium Ions," Academic Press, New York, N.Y., 1971

126. H. Paulsen Advan. Carbohyd. Chem., 26, Academic Press, New York, p. 127, 1971.

127. J. Lenard, Chem. Rev., 69, 625 (1969).

128. L. Goodman, Advan. Carbohyd. Chem., 22, 109 (1967).

129. S. Hunig, Angew. Chem., Int. Ed. Engl., 3, 548 (1964).

130. M. S. Newman and C. H. Chen, J. Org. Chem., 38, 1173 (1973); J. Amer. Chem. Soc., 94, 2149 (1972).

131. M. S. Newman and C. H. Chen, J. Amer. Chem. Soc., 95, 278 (1973).

132. M. S. Newman and D. R. Olson, J. Org. Chem., 38, 4203 (1973).

133. B. T. Golding, D. R. Hall, and S. Sakrikar, J. Chem. Soc. Perkin I., 1214 (1973).

134. A. A. Akhrem, V. V. Zharkov, G. V. Zaitseva, and I. A. Mikhailopulo, Tetrahedron Lett., 1475 (1973).

135. S. Hanessian and E. Moralioglu, Can. J. Chem., 50, 233 (1972).

136. T. P. Culbertson, J. Org. Chem., 38, 3624 (1973).

137. S. Winstein and R. E. Buckles, J. Amer. Chem. Soc., 65, 613 (1943).

138. R. Boschan and S. Winstein, J. Amer. Chem. Soc., 78, 4921 (1956).

139. H. Baganz and L. Domaschke, Chem. Ber., 91, 653 (1958).

140. H. Paulsen and H. Behre, Chem. Ber., 104, 1264, 1281, 1299, 1311 (1971).

141. H. Paulsen, W. P. Trautwein, F. G. Espinosa, and K. Heyns, Tetrahedron Lett., 4137 (1966).

142. H. P. M. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, Tetrahedron, 23, 2315 (1967).

143. R. Mengel, unpublished results.

144. R. N. Lacey in "The Chemistry of Alkenes," Ed. S. Patai, Interscience, London, 1964, p. 1168.

145. Y. Fouron, unpublished results.

146. S. M. McElvain and D. Kundiger, Org. Syntheses, 23, 45 (1943).

147. S. M. McElvain, R. L. Clarke, and G. D. Jones, J. Amer. Chem. Soc., 64, 1966 (1942).

148. H. Staudinger and G. Rathsam, Helv. Chim. Acta., 5, 645 (1922).

149. S. M. McElvain and W. R. Davie, J. Amer. Chem. Soc., 73, 1400 (1951).

150. S. M. McElvain, Chem. Rev. 45, 453 (1949).

151. D. Borrmann in "Methoden Der Organischen Chemie," Band VII/4, Souerstoff-Verbindungen II, Tiel 4, Georg Thieme Verlag, Stuttgart, p. 340, 1968.

152. S. M. McElvain and G. R. McKay, Jr., J. Amer. Chem. Soc., 78, 6086 (1956).

153. S. M. McElvain and D. Kundiger, J. Amer. Chem. Soc., 64, 254 (1942).

154. L. Claisen and E. Haase, Ber., 33, 1242 (1900).

155. M. J. Robins, Y. Fouron and R. Mengel, J. Org. Chem., 39, (1974), in press.

156. A. Kivinen in "The Chemistry of Acyl Halides," Ed. S. Patai, Interscience, London, 1972, p. 221.

157. J. N. Brown and L. M. Trefonas, Organic Preparations and Procedures, 2, 317 (1970).

158. M. MacCoss, unpublished results.

159. C. A. Dekker, J. Amer. Chem. Soc., 87, 4027 (1965).

160. A. Guzmán, P. Ortiz de Montellano, and P. Crabbé, J. Chem. Soc. Perkin I, 91 (1973); P. Crabbé and A. Guzman, Tetrahedron Lett., 115 (1972).

161. V. I. Borodulina-Shvets, I. P. Rudakova, and A. M. Yurkevich, Zh. Obsch. Khim., 41, 2801 (1971).

162. M. J. Robins and R. K. Robins, J. Amer. Chem. Soc., 87, 4934 (1965).

163. J. H. Bowie, S. O. Lawesson, G. Schroll, and D. H. Williams, J. Amer. Chem. Soc., 87, 5742 (1965).

164. S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and

J. A. McCloskey, J. Amer. Chem. Soc., 92, 2510 (1970).